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THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF
THE NATIONAL TUBERCULOSIS ASSOCIATION

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10637

VOLUME XV
JANUARY - JUNE, 1927

PUBLISHED MONTHLY
AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

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THE COMMUNICABILITY OF TUBERCULOSIS IN ADULTS[1]

GAETANO RONZONI[2]

Clinical observation and the statements of anatomists prove that tuberculous infection in the human adult, in a large proportion of cases, takes on a latent form, which may be revealed only by the cutaneous reaction. Granted that systematic investigations made on large numbers of apparently healthy individuals are few in number, the results arrived at by many authors end in complete accord in this respect. My personal researches on individuals from 20 to 40 years of age, as Director of a Diagnostic Centre and in connection with a military commission from 1916 to 1918, led me to conclude that the proportion of latent cases is from 30 to 32 per cent, a proportion that is lower than averages given by other authors (45 to 55 per cent), the differences being due to the organization and special aims of the Service.

The period of latency usually begins at the end of adolescence and increases progressively toward adult age. Among school children in Milan, L. Négri gives figures which vary from 16.46 per cent in the sixth year to 79.44 per cent toward the twelfth year; all else being equal, these figures correspond to the indications furnished by the adult population.

The adult, in a state of latency of his tuberculosis, presents all the appearances of health. When he becomes tuberculous, it seems that one could affirm that it is a question of a new infection. Pursuant to the laws that we shall examine further on, this new infection is what will determine later the progress of the varied and quite diverse symptoms of the disease. Experimental indications, biological tests, anatomical and clinical data, and statistics are in accord in establishing the fact, for those countries enjoying our usual conditions of existence, that tuberculosis in the adult is evidently distinct from the foci of tuberculosis established in infancy.

[1] An address on the clinical subject, *The Part Played by Contagion in Tuberculosis in Adults*, delivered at the Fifth Conference of The International Union Against Tuberculosis, Washington, D. C., September 30, 1926.

[2] Professor of Medicine, University of Milan, and Director of *Istituto di Tisiologia*, Milan, Italy.

The conception that, in countries where the disease is endemic, tuberculous infection in the adult should be considered as a late *reinfection* (or, rather, following a more exact modern term, *superinfection*) of a body already infected in early life by the tubercle bacillus, and partially immunized following this primary infection, is actually a classical idea in the study of phthisis (Behring, Calmette, Sanarelli).

Theoretically, these superinfections may have two origins. They may arise from the exterior, as through infection, like the initial infection (*exogenous superinfection*); or they may also come from a latent focus of bacilli established during the first years of life in the depths of the tissues, this focus being disturbed through modifications in the organic resistance of the individual, to then reawake and lead to the infection of the body with the bacilli that it contains (*endogenous superinfection*). In the latter case, tuberculosis in the adult would be the expression of a relapse or exacerbation; and the foci, newly established at any period of life, are the expression of the mobilization of preceding infections. These, therefore, are true bacillary metastases.

These two conceptions are distinct and clearly opposed. On the basis of experimental contributions, clinical, anatomical and social, which have hitherto been collected, the majority of phthisiologists admit that both mechanisms are represented in tuberculosis of the adult. Those who support one theory to the exclusion of the other are few. However, agreement is lacking among authors when it comes to the question of evaluating the practical predominance of one or the other mechanism and the conditions under which they appear. An endogenous origin is admitted to be a predominant factor in tuberculosis of the adult by Pepere, E. Maragliano, A. Campani, Marfan, Küss, Bezançon, Turban, Römer, Hamburger, Opie, L. Bernard, A. K. Krause, Freymuth, Ranke, Selter, Fishberg, Baldwin, Gardner, Ulrici, Marchand, Hübschmann, Ritter, M. Lange, Röpke, etc. Exogenous superinfection, on the contrary, is considered most important by Roger, Sergent, Aschoff, Braeuning, Raiche, Hayek, Beitzke, E. Albrecht, Hillenberg, Schmorl, Abrikosoff, v. Hansemann, Reichenbach, Hart, Puhl, W. Blumenberg, etc.

The great number and the prestige of the authors cited demonstrate the great interest aroused in the medical profession by the problem. This interest is all the more evidence that the solution constitutes not merely an answer to a problem of considerable scientific importance, namely, that of the pathogenesis of tuberculous infection in adult age,

but equally permits us to draw practical conclusions concerning the individual and group prophylaxis of tuberculosis.

In fact, according to the predominance of one or the other of these theses, the problems of prophylaxis at home, at work, or in sanatoria, etc., take on a different aspect. For example, one can arrive at measures such as those practised at the Infants' Clinic of Gratz, where the infants with negative cutaneous reactions are placed in special rooms, while those with positive reactions are left in the general wards without regard to their proximity to patients who are coughers and bacillus-carriers; for one then admits that the immunity to superinfection conferred by a primary infection is sufficient to render every special rule of prophylaxis superfluous (cited after Braeuning).

Do we, in the actual state of our knowledge, possess sufficient data to solve the problem? It is indisputable that tuberculous infection in the adult can have an endogenous origin. This is demonstrated by the presence of the bacillus in the systemic circulation and the appearance of localizations in certain organs (the eye, for example), where the presence of the bacilli can be explained only by conveyance by the blood. If one examines the mechanism of infection of different organs (in so far as extrapulmonary tuberculosis is concerned), the problem does not appear to present difficulties with respect to the mechanism of the production of the lesions. In the latter case, the infection may be considered as the resultant of metastatic infections arising from preëxisting foci in the body and of dissemination principally by the circulation. It only remains to determine the causes and circumstances that produce these metastases and their localization. It is correct to observe, however, that extrapulmonary tuberculosis, considered as a disease, is rare in the adult; in the institution of which I am director, it has been encountered in only 5.6 per cent in a sum total of 10,000 ambulatory patients, an indisputable adult origin being susceptible of proof in only 2.7 per cent of cases.

The question becomes intricate in so far as pulmonary tuberculosis is concerned, a type infinitely more common and important from all points of view among the tuberculous infections supervening in the adult. It is to this type that I shall confine myself particularly in the course of this report.

The problem cannot be solved directly. Here again, as with all other medical problems, one can only arrive at satisfactory conclusions by examining the situation from the experimental, anatomical, clinical and

social viewpoints. If, in our climates, one admits that pulmonary tuberculosis is most frequently the result of a superinfection, it remains to determine:

1: Whether this superinfection is caused by the reactivation of an old focus, frequently formed since early life and not reabsorbed, or of a new deposition of bacilli of exogenous origin.

2: For what reason and by what mechanism the superinfection supervenes in both cases.

3: What mechanism produces it the most often in practice.

To solve these problems, the point in question is to determine the conditions under which the adult happens to be with regard to tuberculous infection. We can distinguish, in this respect, two biologically different groups; namely, (1) adults exempt from tuberculous infection and therefore constituting virgin soil, and (2) adults living in the midst of endemic tuberculosis.

TUBERCULOUS INFECTION IN ADULT MEMBERS OF MORE PRIMITIVE CIVILIZATIONS

With regard to tuberculosis these human groups may be considered like experimental groups. They are unaffected organisms vulnerable to infection up to adult age; in the latter case, it can be admitted to be a case of primary infection.

It is to Calmette and the French school (Parrot, Folly, Mesnard, Moreau, Borrel, etc.) that the credit belongs for having studied and defined the peculiarities of this group in a manner that allows us to-day to consider the question as solved.

The known observations may be classed in the following manner:

1: Observations, before the war, relating to countries free from tuberculosis and individuals or human groups infected by Europeans or tuberculous natives.

2: Observations, during the war, relating to unaffected individuals transported in troops to where the bacillary infection prevailed.

With the first group are connected principally the observations gathered by Calmette on Negroes in the course of an investigation on the natives of the French colonies, with the aim of establishing the importance and diffusion of tuberculosis in different climates. The method of investigation is based on the cutaneous reaction. The successive

reports on this question only confirm the information of the French master.

The investigations and researches made in connection with these ideas have demonstrated that:

1: In regions, isolated by their geographic situation or any other cause, and among peoples who live distant from all civilized crowding, tuberculosis is lacking or tends to be extremely rare; these populations escape a tuberculous infecton that is almost obligatory in our countries by virtue of our social organization.

2: However, when these groups or individuals happen to come in contact with the bacillus, they show an exaggerated susceptibility to contract tuberculosis. Neither a climatic immunity nor a racial immunity can be recognized.

3: In these adult individuals the tuberculous infection possesses characteristics clearly different from the manifestations currently observed among ourselves. In the great majority of cases, it appears as an acute illness, with the characteristics that we have been accustomed to seeing in infants, whether from a clinical or an anatomical viewpoint (absence of fibrous reactions, proneness to rapid generalization, death in a short period).

So far as concerns the observations during the war, it is necessary to emphasize particularly those of Borrel on the Senegalese transported to France. These data have been successively confirmed by C. Blazy and Ch. Rouvier. Borrel's observations show how tuberculous infection in the Senegalese, rare in the first year of the war, broke out suddenly with grave symptoms during the second year. The disease appeared with symptoms of a massive and rapid infection, its spread being facilitated by crowding, living together, bad habits of hygiene, and the delay of the soldiers in reporting to the doctor until the disease was advanced. The infection almost always began with the characteristics of an acute disease, without marked respiratory symptoms, but with a predominant infection of the lymphatic system, frequently radiating from the hilum to the lung and often to the axillary region, and characterized finally by a rapid evolution (death in three or four months) caused by the generalization of the infection in the lungs, serous cavities and spleen, while one frequently noted the absence of bacilli from the expectoration. At necropsy, the character and distribution of the lesions enabled one to retrace the evolution of the disease; that is, there were caseous tracheobronchial nodes of various sizes, and chains of nodes, frequently infiltrated, extending from the hilum to the axillary fossa. These lesions

show the character of the primary infection and the point of separation of the rapid diffusion in the body by rupture of the lymph-node barrier and the invasion of bacilli through the lymphatic and blood channels. Only in exceptional cases was chronic pulmonary tuberculosis observed by the author.

Borrel's findings have been confirmed by C. Blazy. The author was able to establish the fact that the infection almost always coincided with the arrival of troops in France, and that it could be considered as the result of the urban life. He observed to the same extent the rarity of chronic pulmonary tuberculosis (5 per cent) and the frequency of acute symptoms (tracheobronchial adenopathy 80 per cent, caseous pneumonia 30 per cent, and generalized miliary 25 per cent).

Against these statements some authors have objected that it is really less a question of primary infection in the modern sense of the word than of special reactions due to race, which are capable of modifying the clinical and anatomical evolution of tuberculous infection as it occurs in the white man. For my part, I cannot admit this explanation, as it does not correspond with observed facts. The difference between the two human types is not explained by the terrain, but by the conditions of infection. The native is usually not exposed to infection in the same manner as the white man. Tuberculous infection does not strike him from the first years of his life, as in the case of the white man; he often escapes it until adult age. The proof that this is not a question of race is furnished by the Negroes who, having lived for a long time in contact with white people, acquired analogous peculiarities against tuberculous infection. The American Negro, acclimated to civilization, contracts chronic tuberculosis, while the African Negro, exposed late and individually to the infection, contracts tuberculosis which progresses according to the characteristics of tuberculous infection in early infancy. Thus it is that in Philadelphia, despite the large proportion of blacks, tuberculosis is on the decrease, as in the other States of North America. This is due in large part to the admirable antituberculosis organization of the United States, resulting from the coördinated efforts of the States and of private endeavors (Horvood).

These facts relating to natively unaffected races can be observed, though in a more limited manner, in our actual civilization. Despite the constant ubiquity of the bacillus in our midst, special circumstances may cause individuals to live far away from crowded populations; thus they will remain free from infection. They contract the infection at

an adult age like the races that have remained in a condition to constitute virgin soil.

Klotz, cited by Borrel, reports that American soldiers of the white race coming from the great regions isolated from the centres of population, where they lived as wanderers, were able to escape contact with the bacillus and, after being recruited, presented primary infections. Austrian military physicians observed that the majority of cases of acute tuberculosis diagnosed in the old imperial army came from Bosnia and Herzegovina, countries where pulmonary tuberculosis was rare. In my duties with the Diagnostic Centre, and the Commission of the Army Corps of Milan, I was able to observe cases of tuberculosis with rapid progression in those soldiers coming from the isolated and mountainous regions of the Abruzze and Sicily, where tuberculosis is almost unknown. I have made similar statements, confirmed by other physicians, for certain agricultural centres of Lombardy, where communication with the outside is rare and the population remains inbred. Here tuberculous infection was spread in a serious and rapid manner, with acute symptoms, without sparing adult age, and attacking principally women following the return to their families of the soldiers invalided for pulmonary tuberculosis.

To my thinking, one can arrive at analogous conclusions by analyzing the emigration statistics. The Italian emigration problem is exceptionally interesting, not only from the economic but also the hygienic viewpoint, because it is proved that emigration is a factor that increases the proportion of deaths from tuberculosis; and outside of this, from the national viewpoint, it helps to increase the number of tuberculous persons in the same country. The Italians of the southern provinces, where the mortality from tuberculosis is very low, exhibited an increased incidence after their establishment in the great urban centres beyond the Atlantic (Stella, Sestini, Montano and Rosati). Analyzing the interesting statistics published by Stella and Sestini, concerning the reports of tuberculosis connected with Italian emigration to America, Sanarelli is of the opinion that the serious phenomena described should be explained by the lack of immunization of the Italian emigrants in his country, this phenomenon being due to the rarity of tuberculosis in the southern provinces of Italy, whence comes the greatest contingent of emigrants. It is by an analogous mechanism that one could explain the aggravation of the tuberculous illness and the increased mortality following emigration observed for a long time by Italian hygienists (deVestea) in some

centres of southern Italy. Analyzing the subject of emigration with reference to tuberculosis and its interpretation, it is wise, however, to be prudent and examine the facts from all angles. Although the observations gathered seem to indicate that it is a question of a general phenomenon of lack of immunization analogous to that observed at the time of emigration from the country to the cities, one cannot, however, exclude other factors which may contribute to the increase of pulmonary tuberculosis in the course of emigration (fatigue, mental strain, privations, etc.).

The facts cited demonstrate that, even under normal conditions of social life, various cases are established, in which the lack of resistance to tuberculous infection is perceived and in which the infection develops at an adult age following the modalities of a primary infection. In the latter case, the problem is not presented in such an apparent, almost experimental, manner, as in the races free from the disease, because it is necessary to consider the smallness of the regions whence the patients come, the lack of anatomical evidences, and the inevitable proximity of unaffected and infected individuals.

To this group of observations, in my opinion, belong equally the rare cases of primary tuberculous infection of adult age reported in the literature.

We should separate from this group certain exceptional and almost experimental cases. The typical example is that of Tappeiner's servant, cited in all the classical works. In this case, as well as in some similar other ones, it is a question of observations in which the mechanism of infection has no relation to those observed during the ordinary course of life.

On the other hand, different clinical and anatomical findings are recognized in support of the hypothesis of a primary tuberculous infection in adult age which, though rare, could be observed in the normal conditions of our civilization (hypothesis supported by A. Cain and P. Hillemand).

Statistics on the spread of tuberculosis in civilized countries present marked differences, according to the writers, as we know. There are many reasons for this (the source of the material observed, the age, etc.). Negative cutaneous reactions vary from 10, 15 and 18 per cent to 3 and 4 per cent. These variations correspond to the differences in the statistical and anatomico-pathological data. The observations

made by the institution of which I am Director furnished an average proportion of 12 per cent, in so far as adults are concerned. One can state on the basis of these publications that, of one hundred individuals past the age of 20 in our midst, one could not actually find more than seven or eight who have not yet been touched by the bacillus (Calmette). These figures, which prove the enormous spread of tuberculous infection in civilized countries, equally prove that the infection does not strike the whole adult population. There is always a certain remainder of persons who appear refractory to the infection. These conclusions give rise to some perplexities; but they are not enough to lead us to recognize, however, the existence of a natural immunity in the human species.

In fact, it seems difficult to admit, in the actual state of our knowledge, that, under the usual circumstances of social life, there can be individuals to whom the bacillus cannot gain entrance either by the respiratory or intestinal route. One may think that certain individuals possess in their bodies sufficient means of protection to combat an infrequent and scanty absorption of bacilli, but laboratory findings and experimental and clinical researches do not allow us to consider this hypothesis as certain. One could equally think of a refractory state to every new infection following immunization as a result of a preceding infection. As we shall see later, these findings accord ill with each other. Immunity to tuberculosis is not transmitted passively. The "antibodies," which can easily be detected in the newborn issue of a tuberculous mother, tend to disappear rapidly from the circulation (Léon Bernard). Cain and Hillemand think of the possibility of an immunity coming from the tissues; this hypothesis, however, has not yet succeeded in gathering sufficiently sound, scientific support.

A critical examination of the information that we possess shows that the individuals in question are susceptible to contract tuberculosis at a given time, although there may be no apparent change in the dangers of infection that they incur. In the actual state of our knowledge, it is impossible for us to understand what causes this change. It is probable that all the causes which diminish bodily resistance, and cause asthenia in tuberculous persons, are equally capable of facilitating a late fixation of the bacillus. The data furnished by cutaneous reactions (for example, in the infants vaccinated with *BCG*, according to the reports of Calmette) lend some color of probability to this idea.

In these patients also, one cannot exclude the possibility of a benign infection, due either to individual resistance or a small dose of bacilli

absorbed. In the latter case, the disease appears to acquire a chronic character, following the same mechanism that we shall explain later. It may be a question here of a case devoid of clinical symptoms, and discovered only by a positive cutaneous reaction.

It is not rare, however, to note the acute progress of the infection. The observations of A. Cain and P. Hillemand, deLemière, Kindberg and L. Bernard are conclusive in this respect. It is necessary, however, to recognize the fact that it is frequently very difficult in practice to prove that these symptoms result from a primary infection. The family history of the patient, the interpretation of which is difficult, acquires value only when it is possible to specify the source of the infection. It is not always easy to apply the cutaneous reaction in a series with a view of determining the time of the transformation from the negative to the positive phase. One must accord great value to the anatomical facts established by certain writers, when they instance the same lesions as those established in the infant, which we have cited in connection with tuberculosis of natively unaffected races. One must attach great importance to the absence of old tuberculous lesions, observing, however, that if the exclusion of these symptoms is relatively easy and conclusive as regards the caseous and miliary forms of tuberculosis, since the examination of the lungs is then relatively easy, one cannot have the same security as regards bronchopulmonary tuberculosis. In the latter case, it is necessary to resort to exact histological examinations, made in series, and the absence of old lesions can be stated only with great reserve.

In every way, likewise, in this group of cases, it is impossible to come to the conclusion that there is an immunity to tuberculous infection, but only a greater resistance to this infection. This resistance is perhaps constitutional, and, still more probably, linked to special conditions in which the infection takes place.

From these facts, one can draw the following conclusions:

1: When, in races free from tuberculous taint, the infection breaks out and develops at adult age, it usually presents the characteristics of a primary infection.

2: The peculiarities are not connected with the race, but should be attributed to the fact that the organism lacks protection against the infection.

3: If one may accept some observations gathered in the literature, to the effect that, under the usual conditions of life, a certain number of individuals can remain unaffected and escape tuberculosis until adult age, a critical examination of these observations, in my opinion, allows us to exclude an im-

munity in the absolute sense of the word. These individuals, when exposed to infection and suffering a diminution of their bodily resistance, may acquire a tuberculosis that seems to develop almost always with the characteristics of a primary infection.

THE ADULT IN COUNTRIES WHERE TUBERCULOSIS IS ENDEMIC

As has already been said, the normal adult in 92 to 93 per cent of cases is found in a latent condition of infection.

The first infection takes place, as we know, during early life, and results from contagion. Every individual is predisposed to the infection, and *pretuberculosis* is an inadmissible term from a scientific viewpoint. An hereditary transmission of tuberculosis, while remaining entirely possible from a biological viewpoint (experiments of Maffucci), occupies so secondary a place as to be of slight importance from a scientific point of view and may be considered nonexistent from the social viewpoint, in the actual state of our knowledge and observed facts.

Recent discoveries on the variations of types of tubercle bacilli and the existence of a filter-passing tuberculous virus have not yet acquired a sufficiently practical value. The virulence of the bacillus does not present, in practice, those variations that have been observed for pathogenic bacteria in general. From whatever lesion it is recovered, the microörganism displays determined identity (Burnett). All that can be conceded is that the virus, as I showed in 1902, can assume specially adapted forms. The primary infection can be a prolific one, when it has its source in a home environment, or it can be a weak infection when it is accidental. It may be a single, occasional, repeated or prolonged infection, as well as fortuitous, accidental and often cryptic. The infection depends, so to say, on the quantity of bacilli concerned (Léon Bernard). Those that are isolated seem to be inoffensive; Thoeni and Thuyssen, Calmette and Bruyand, Webb and W. Williams, Léon Bernard and Gougerot, etc., have given experimental proof of this. The abundance of the microbes determines, not only the origin of the foci, but also the entire mechanism of bacillary infection and all the consequences of the infection. Against a massive infection the body is unable to defend itself and succumbs; against a weak infection it resists and recovers.

This cure does not resemble that observed for other infectious diseases. In an anatomical and biological sense cure is exceptional. It

corresponds almost always, as we have seen, to a state of latent infection. The germ does not die; it usually remains encapsulated, often in calcified foci, but capable of reproducing itself and, experimentally, of reproducing the disease.

Therefore, one must consider, in the adult, the resistance to the infection more than infection itself. The conclusions to which we have come, following recent investigations, may be summarized as follows: As has been seen, it cannot be admitted that there is a natural immunity for the human species resulting from a histogenic or cellular defense. The hypothesis of an immunity of terrain, which would result from a particular biochemical composition of the humors and would determine the arrest of progress of tuberculous lesions, does not rest on a firm scientific basis. Human immunity against tuberculosis is an acquired immunity, a sort of spontaneous vaccination. This state of immunity is demonstrated scientifically by a group of data and facts, although researches undertaken with a view to the immunization of man and animals against tuberculosis have not yet given practical, certain and undeniable results. There arises the question of whether the state of immunity or resistance persists likewise when the body has succeeded in extinguishing the tuberculous focus and obtaining a veritable cure. Calmette, on the basis of solid experimental arguments, declares that the immunity lasts only as long as the tuberculous focus contains living bacilli, while clinically it remains entirely quiescent. If complete cure supervenes, we shall see, as in syphilis, a new infection taking place with characteristics identical with those observed on virgin soil. The cure makes the body lose that special state of resistance which constitutes immunity to infection. Moreover, an anatomical cure of human tuberculosis is, according to Calmette, a decidedly exceptional eventuality.

Superinfection, endogenous or exogenous, therefore, finds a modified terrain in the adult, a state of allergy. This view is confirmed by clinical observations on the favorable progress of cutaneous forms (such as anatomical tuberculosis and verrucose tuberculosis, undeniable forms of exogenous superinfection, according to Liebermeister), on lupus and on the very small proportion of laryngeal localizations (Agazzi). It is equally confirmed by the recent very interesting experiments of H. S. Willis on the manner of spread of the tubercle bacillus in the guinea pig, reinfected by the cutaneous route; also by those of Lagrange on the limits of ocular infection following an intravenous superinfection.

The allergic state, however, varies with each individual. It is unstable and subject to many influences often impossible to specify. Nevertheless, it seems able to defend the body against further invasion by the tuberculous virus. It is this allergic state which, combined with the number of infective bacilli, determines the course of a superinfection.

The method by which the allergic organism reacts against the bacillary infection may be interpreted in different ways; nevertheless, the fact itself remains. According to Römer, the body tolerates the reinfecting germs as if they were inert; according to Calmette and Guérin, these germs are eliminated; according to Rist, they are destroyed by a phenomenon of lysis analogous to the Pfeiffer phenomenon; according to Nicolle, the tuberculous antigens are neutralized by antibodies.

Tuberculous infection in man (including here superinfection) is facilitated or impeded by various influences: for instance, conditions of infection (quantity, virulence, dead or living bacilli, bacilli associated with other germs); more or less intimate contact between the germs and the tissues; the nature and histology of the tissues. The following states in their terminal stage predispose to the infection: namely, lymphatism (in the modern sense of the word), prolonged anemia, excessive intellectual or physical effort, chronic intoxication, malnutrition, unhygienic dwelling conditions, habits, and routine, etc. These factors, however, do not constitute a specific predisposition. The doctrine of predisposition to tuberculosis, whether associated with a terrain of inferior hereditary resistance or a particular age, or considered in connection with the endocrine factors on which the hormonic equilibrium depends, is a question that has undergone complete revision in recent years. The observations of Raiche, confirmed by Brolette, based on a statistical survey of cases of pulmonary tuberculosis covering a long period, confirm the clinical and biological rule, according to which a tuberculous heredity does not have an essential influence on the progress of the disease in the descendants. In the majority of cases, these patients owe their disease to the infection to which they have been constantly exposed rather than to their ascendants. Moreover, admitting the important influence of environment on tuberculous infection, one cannot deny the fact that under identical circumstances certain individuals are infected and others not; that, among those who are infected, some oppose an energetic and decisive defense to the bacillary invasion, while others behave inertly; and that the latter generally have a tuberculous ancestry. These facts can be interpreted, in all probability, as indicating a diminu-

tion of local and general resistance to the disease. Anatomical investigations, as Pepere has correctly observed, have lessened the importance, accorded by general agreement until now, to certain skeletal or somatic peculiarities, to which, however, the doctrine of constitutional predisposition tends to-day to ascribe a partial validity (DeGiovani, Maragliano, Lucatello, Viola, Fici). On the other hand, in opposition to the statements of the extreme believers in contagion, let us recall that truth is found in a happy medium, and that it is necessary to recognize the importance of those constitutional and congenital factors, whatever they may be, that are conducive to the infection and offer the tuberculous virus the best opportunities of implantation and development.

This exposition will make one appreciate the polymorphous character of the pulmonary tuberculous infection, most especially in the adult, from the threefold clinical, anatomical and progressional viewpoint. This polymorphism is likewise one of the characteristics of the tubercle bacillus, always identical but variable in its effects, by reason of the abundance of the infection and the specific resistance of the individual.

Experimental Results

In the experimental study of tuberculous superinfection, the majority of authors start from Koch's phenomenon based on the actual conception of acquired immunity to tuberculous infection. The facts which characterize this phenomenon have been confirmed by all who have repeated this experiment; namely, (1) the proof in the guinea pig of the immunity to a mild tuberculous infection; and (2) the attenuated virulence of stronger doses.

Koch's phenomenon occurs in a typical form only when the severity of the primary infection and the interval between the first and second inoculations are included within certain limits. If the primary infection is too severe or the dosage of the second inoculation too strong, death rapidly supervenes (by a mechanism analogous to that of the tuberculin reaction).

Following the majority of authors, and, among the Italians, Micheli and Zironi, the result of experiments undertaken on various species of animals is that it is impossible to obtain experimentally an absolute immunity to tuberculosis. Neufeld recently insisted (1923) on the fact that not only in the guinea pig, a hypersensitive animal, but also in the sheep (which is closer to man with respect to allergy and sensi-

tiveness to tuberculin), the defense conferred by a first infection against a reinfection of medium intensity is proportional to the quantity of infectious germs and the time elapsing between the two inoculations. On the other hand, the work of Allen Krause proves that, conditions being equal, the age of the animal in the experiment has no appreciable influence on the resistance. It would seem (and, to my thinking, this idea would be of capital importance if it were confirmed) that the immunity of a tuberculous guinea pig to reinfection is much less marked when the animal is inoculated with bacilli coming from its own lesions (Paraf).

All these facts lead to the same extremely important conclusion: namely, that we are dealing with a special humoral condition induced by the primary inoculation. (This would be the index of a relative immunization and special sensitization, the allergic state of Pirquet.) The experimental result of this is that it cannot be taken for granted that an animal will have an absolute immunity to reinfection and that this will take place in a given limit of time.

How do the tissues of the infected animal, and particularly his pulmonary tissues, react to reinoculation? The facts, observed in the course of Koch's phenomena, the writers repeat, consist in the infiltration of the tissues at the site of inoculation, with gangrene, necrosis and ulceration, in order. In the lungs, rapid and extensive caseous necrosis is often observed and, at times, the formation of cavities (an evolution similar to that which occurs in man). Let us add, however, that the opinion, according to which rapid necrosis of the cutaneous and pulmonary tissues would be an index of the hypersensitiveness to the bacilli and their poisons, is not accepted without argument. According to certain authors, Koch's phenomenon would be connected with the group of manifestations of immunity. They consider the rapid elimination of tubercle bacilli contained in the necrotic tissues and the cure of the cutaneous focus as indices of the greater resistance acquired by the animal carrying a chronic tuberculous lesion, as compared with the healthy animal. In support of this interpretation, one can cite the results obtained after numerous experiments, principally those of Calmette, Borrel, Römer, Hamburger, Finzi, etc. These investigations are in accord, to prove by different procedures that, by reinoculating animals affected with chronic tuberculosis, preferably with large doses of virulent bacilli, one manages to obtain with difficulty a diffuse, rapidly progressing infection.

Despite the uncertainty that exists as to the interpretation of the experimental results and despite the extreme difficulties in the way of explaining human visceral tuberculosis in accordance with these data, the experimental fact remains established that, in an infected animal, the tuberculous superinfection determines, even in the lungs, a more or less extensive specific infiltration accompanied by necrosis.

The lesions and experimental reactions in question are obtained by inoculating guinea pigs by the subcutaneous, serous or intravenous route; and here one should recall that the results obtained by these indirect methods support the theory of endogenous superinfection.

Certain authors have tried to solve the problem by the direct method by studying the effects of experimental tuberculosis on the animal infected by the respiratory routes. The recent very interesting investigations of A. Philibert and F. Corday on experimental tuberculous reinfection in the adult rabbit by the tracheal route have proved that by this method, when large doses are employed, extensive caseous lesions in the lungs with the formation of cavities are obtained. The experiments of these French authors confirm those of E. R. Baldwin and L. U. Gardner. The latter workers showed how guinea pigs cured of primary infections contracted by the respiratory route (cure strictly verified) could be experimentally reinfected by inhalation. This method, however, requires large doses of bacilli.

In these experiments, dosage of bacilli is very important, without, however, having an absolute value. Taking as basic their studies and investigations on the dose necessary to inoculate a guinea pig with tertiary tuberculosis, the authors are generally in accord in recognizing that the dose required to produce an exogenous infection is so large that it is not found under the ordinary conditions of life. On the other hand, Beitzke proved that, by making a count of the residual contents of the primary focus and the consecutive secondary metastases in a primary pulmonary infection, one does not succeed in obtaining a sufficient quantity of bacilli to produce a massive reinfection. It should be mentioned, however, that Hippke, Braeuning and Hillmann have given evidence by varied but concordant experiments that one frequently encounters the practical possibility of a superinfection, because the droplets expectorated by a phthisical patient often contain a quantity of germs sufficient to immunize a guinea pig under normal conditions (1 to 100 bacilli). One can no longer exclude the possibilities of an exceptional quantity of bacilli (5000 and more), a quantity more than

sufficient to induce a massive infection, reaching in an unfavorable case either the ultimate ramifications of the respiratory passages or a sensitive point in the skin or mucous membrane. Finally, Neufeld made the observation that the idea of a massive infection should be understood in a relative sense. Individual resistance to superinfection is subject to great variations in man as well as animals. Factors such as unfavorable social conditions, poverty and bad habits of hygiene should be taken into consideration when the question of estimating the minimal dose of germs necessary to produce a superinfection comes up.

The experiment, comprising guinea pigs placed in a hospital ward in the vicinity of a phthisical patient (even if the room is perfectly clean and free from dust), to prove that they contract tuberculosis with exceptional ease, according to the mechanism illustrated by Flügge, is not, to my mind, conclusive. One cannot draw conclusions for man from such a procedure. If one bears in mind the clinical and epidemiological observations of Baldwin and Gardner, confirmed by investigations which I made personally at the Medical Clinic of Pavia in 1902 and 1903, and confirmed also by dispensary practice and the observations on the epidemic episodes of the disease in the sanatoria (where special precautions are taken to prevent direct contact through dust or food, but where it is impossible to eliminate the danger caused by droplets of mouth spray), one will be convinced that the outcome of a massive infection of the adult by the respiratory passages is extremely restricted, but that it would be able to exercise a limited action on the superinfection, such as is established naturally in a human environment. If exogenous infection is possible, it can only be admitted on an experimental basis for medium or repeated minimal doses.

For this exposition, one can draw the following conclusions: Experimentally, early but mild and not repeated infection confers on the body a resistance sufficient to defend itself in case of further reinfection against the serious and progressive forms of the disease.

The animal exposed later to repeated and massive infection exhibits its resistance to reinfection by local tuberculous lesions which do not delay in suppurating (cavity, cold abscess, etc.).

These reactions are observed no matter what the route followed by the superinfection. It is necessary to remember, however, that, in the case in which the reinfection takes place by inhalation, it involves doses of tubercle bacilli such as are presumably met with only exceptionally in human environment.

Exogenous superinfection should, then, be considered from the experimental point of view as less simple and less common than the other form.

Results of Anatomical Investigation

If the tuberculous virus can invade the body by all organs that are directly or indirectly in relation to the external world, the most common and most important route is the intestine, and, still more so, the respiratory apparatus. The aerogenous or inhalatory theory, already supported in Italy by Mantegazza, Verga and Biffi, is, from the anatomical as well as the clinical viewpoint, the one that prevails over the others.

The anatomico-pathological basis of the primary tuberculous focus in the nursling and infant, already depicted by Petruschky in 1897, has actually become classical, thanks among others, to the investigations of E. Ranke, A. Ghon and his school, Ribbert, Tendeloo, Comby, Opie, Comba, di Stefano, Spolverini, etc. This primary focus, in the modern sense of the word, includes not only the consecutive changes to the local reaction in the pulmonary tissues of the healthy individual at the point of penetration of the bacillus in the tissues, but also the changes in the lymphatic network of the region near the point of inoculation as well as the regional lymph nodes. The ensemble of these elements represents the primitive lesion of the anatomists. This lesion possesses certain characteristics that allow the anatomist to distinguish it almost to a certainty, even after an extended period, whether it is in the lungs or the lymph nodes. The transformations of the lymphatic system, in the sense of a local calcification, are of great importance for the establishment of a diagnosis of "old lesion of pulmonary tuberculosis." Even when one bears in mind the reservations, from the anatomical point of view, of Beitzke, Liebermeister and other authorities, Ranke's definition continues to express the exact interpretation of the anatomical facts by the general law: "The foci of calcification in the lymph nodes of the hilum and in the lung are, in the great majority of cases, the isolated expressions of a primary tuberculous lesion."

Admitting that the primary focus can remain limited and circumscribed for a certain time, it has a tendency, due to the particular histology of the tissues in question, to enlarge locally by the progressive invasion of lymphatic vessels in the vicinity of the point of inoculation. The changes in the local lymphatic system quite rapidly assume a predominant importance. It is not superfluous to indicate here these borrowed data,

and also others as related so lucidly last year to the Provincial Anti-tuberculosis Congress by Professor Pepere of the University of Milan. We shall frequently return to this later.

Thus considered, the primary tuberculous lesion should correspond with quite different phenomena, according to the case. Its multiplicity, the extension taken by the primary pulmonary focus, the corresponding invasion of lymphatic vessels, the more or less considerable participation of the lymph-node group, and the different methods of propagation of the lesion, which progresses either in stages or a continuous manner, are likewise varied and variable factors.

It will be understood, after what has gone before, that one does not always observe an exact correlation between the clinical perception of the initial tuberculous lesion and its anatomico-pathological significance. The lesion can remain latent for a long time without apparent clinical symptoms. Often a malady, which clinically appears incipient, has, from the anatomico-pathological viewpoint, already largely passed the primary period, even if this term is taken in the broadest sense. This detail is not receiving the biological and practical importance of exact ideas concerning the first stages of the infection.

The primary lesion, once established, may progress either in the sense of a real or apparent cure (otherwise called latent period) or toward progression of the disease to the second degree. The discovery of initial tuberculous lesions, cured or on the way to cure, is very common, as has been seen, according as one grows older; and it attains quite a high percentage in the adult, which fact proves (and here all the writers are in accord) that man contracts the infection easily, and that the infection is more common than the disease. In Italy, Pepere found in Pisa, a city greatly decimated by tuberculosis, that 71 per cent of necropsies on people dying of general diseases revealed cured tuberculous lesions; in Pavia, the proportion stated by A. Monti is 83 per cent.

Anatomical and biological cure of the primary lesion, partial or complete, is an admissible thing. Experience proves it in a certain number of cases. This cure is similar to that observed in the foci of pulmonary tuberculosis treated by artificial pneumothorax (Forlanini, Carpi). It would, however, be erroneous to regard as a cured tuberculosis all the centres of calcification or cicatrization found in the lung. The repair of a circumscribed tuberculous focus is limited, like the local infection itself, and is often only apparent. This idea is of fundamental importance in the thesis that we are supporting. The facts which are going

to be cited, although they are of unequal value, confirm the frequency at all ages of an activity of the primary lesion (V. Hansemann, Kossel, Weber and Heuss, etc.).

Schmitz states that he has discovered living and virulent bacilli in 75 per cent of old primary lesions. And this is not all. Recent exact histological observations by H. Sieger prove that the primary lesion, pulmonary as well as lymphatic, is not so certain an element that one can exclude in this respect all possibility of endogenous superinfection.

The first question that comes up, and it is of great interest for our thesis, is the following: Is the passage from the primary to the secondary state possible in the adult? Anatomical investigations permit an affirmative answer. In this connection, there is always occasion to remark that the evolution of infections from the state of primary latency to the secondary stage is, in a general manner, more complex than anatomical observations disclose. Between one and the other stage there is always at some time a longer or shorter interval of time, which is revealed to us by the anatomical characteristics of the initial lesion, constituting manifest indices of a more or less ancient process with respect to the metastases and recent diffusions. The result of this is the very important fact for our thesis that the period of latency is often marked by the return of activity either in the primary focus not yet extinguished, in the regional lymphatics, or in these two elements together, followed by new phases of latency of the clinically quiescent process, which however still persists in the domain of the primary lesion. These returns of activity can eventuate in cure, or induce in their turn the invasion of new lymphatic regions, and lead sooner or later to dissemination, generalization, and the breaking out of a secondary tuberculosis. Quite recently A. Ghon and H. Rundlich cited six cases, in which the anatomical conditions were clearly favorable to the awakening of a latent primary pulmonary tuberculosis and consequent progression by further extension of an endogenous tertiary tuberculosis of the apices.

In these cases, which have been the object of special studies, the anatomists speak of "relapse," of "endogenous reinfection," and "endogenous lymphoglandular reinfection." Pepere suggests the simpler and clearer expression of "revivification (*réviviscence*) of the primary focus." In this manner the idea is clearly expressed that in these cases the focus breaks out again under the influence of bacilli preëxisting in the organism. The exactness of this view is confirmed, according to the anatomists, by two groups of observations.

The first group is represented by observations on endogenous superinfection, starting from primary lesions, that have remained latent for a certain time and extended in the lymphatico-broncho-mediastinal circle to the last element of the chain constituted by the adjacent system of the venous angle, to invade the blood circulation and induce a reinfection of the lung. In the majority of such cases, the duration and mechanism of this process escapes clinical observation, when a pulmonary tuberculosis is already in the process of being established.

The second group includes the quite rare cases of reactivation of the initial pulmonary focus independently of the participation of the regional lymph nodes. In the course of more than twenty years of practical anatomy, Pepere succeeded in collecting some certain cases, although few in number. The most frequent anatomical picture is a primary focus, remaining in a latent state over a longer or shorter period of time, which is then restored under the influence of a recrudescence of the local infection and progresses toward the tertiary form of phthisis, or which has already reached this stage with ulcerations and the formation of cavities. These facts have been verified not only for the lung, but also for the intestine, with anatomical and histological characteristics that do not allow room for error.

The aggregate of data and of facts recalled above proves in an exact manner that the endogenous origin of the superinfection that leads to tertiary tuberculosis, particularly in so far as pulmonary tuberculosis is concerned, should be admitted anatomically as an established and not exceptional fact.

Other statements, although they are not so decisive, are cited in the literature in support of this doctrine. I have already recalled the investigations and results obtained by H. Siegen, which prove that the primary lesion, even in its lymph-node element, cannot be considered as a focus sufficiently clearly isolated and differentiated from the adjacent tissues to exclude the possibility of a reinfection of the body by means of this lesion. Heilmann has succeeded in making evident small vessels in immediate relation to the capsule of the primary lesion. These facts are of great value in so far as surgical tuberculosis is concerned, for the origin of which one can in general look to no other route than the blood circulation. The case of pulmonary tuberculosis is more complex, for here the possibility and ease of an exogenous infection naturally enter into play. The characteristics which differentiate the primary focus from the focus of pulmonary reinfection have been the

object of the well-known anatomical investigations on the part of Puhl. The characteristics of the focus of pulmonary superinfection indicated are as follows: predominant localization at the apex, relatively great extension, clear demarcation of the pulmonary tissue, relatively rare calcification, and the absence of analogous changes of the same chronicity in the regional lymph nodes. The exogenous origin of the primary focus is not discussed. As Siegen has remarked, why should the focus of reinfection, once established, be separate in its pulmonary origin from the first focus? Why search for another origin for the pulmonary tertiary foci, which should be considered latent rather than cured, when the limiting capsule of the primary focus is not always hermetically closed with respect to the adjacent zone, and the tubercle bacilli are thus separated from the blood by a barrier of variable histological resistance, often incapable, it seems, of resisting simple congestions? Some authors object that the focus of pulmonary superinfection should be considered as having a distinct origin from the primary focus, because it is generally situated at the apex, while the primary focus has no determined localization. It can nevertheless be remarked that this peculiarity could find its explanation in the well-known law of the localization of the focus of reinfection in the predisposed pulmonary areas.

Still we are not authorized to conclude, after what I have pointed out, that every case of tertiary phthisis should be considered from the anatomical viewpoint as the result of an endogenous superinfection. Authors of incontestable merit, such as A. Ghon and H. Kundlich, confirmed defenders of the endogenous theory, do not exclude the anatomical possibility of an exogenous superinfection. W. Blumenberg, in a series of methodically conducted anatomical observations recently published on human tuberculosis at different ages, arrives at the conclusion, which in my opinion is debatable, that tuberculosis in the adult cannot be considered as the second or third stage of a tuberculosis contracted in early life, but rather as a distinct and separate disease, independent of preceding foci for its origin and development.

From the anatomical point of view, one can call upon three categories of facts in favor of exogenous superinfection, as follows: (1) the demonstration of the certain existence of primary lesions biologically cured: (2) the rare but certain demonstration in some cases of pulmonary tuberculosis in the adult of a primary lesion limited to the pulmonary element (the absence of the lymphoganglionic combination would tend

to prove that one can admit for these cases the existence of residues of old infection); and (3) the continuous possibility of an aerogenous infection in the usual conditions of human life.

The conclusions that may be drawn from anatomical observations in the actual state of our knowledge may be formulated as follows:

An entire series of facts in favor of endogenous superinfection of pulmonary tuberculosis in the adult has been the object of exact demonstrations.

If the number and significance of these facts authorize the admission that endogenous superinfection is sufficiently frequent, they cannot, however, allow the conclusion that tuberculous infection in the adult depends on this mechanism alone.

According to data of indisputable value, we should in certain cases recognize the possibility of an exogenous superinfection.

It is impossible in practice to compare and determine the frequency of these two modes of infection. Admitting the two modes of pathogenesis, pathological anatomy does not yet possess decisive data to affirm which of the two predominates and to what extent. Anatomically it is inferred that there is a superinfection without arrest of the pathogenic process, hitherto based first of all on anatomical facts.

Results of Clinical Experience

The clinical demonstration of an exogenous superinfection could be found only in the cases of biological cure. But, as has been seen, such a cure is exceptional and, if one can admit it, can be demonstrated with difficulty in practice.

The clinical observations in favor of an exogenous superinfection are to my knowledge, few and indirect.

Ranke and Sellier, studying the tuberculin reaction in boys (up to 15 years of age) disabled by the war, remarked that the intensity of this reaction bears a direct relation to the possibility of infection and its duration. The intensity of the tuberculin reactions would be proportional to the family crowding with respect to lodgings and the duration of the contact with phthisical persons. In the cases in question, one would find himself in the presence of subjects continually contaminated under the action of new bacillary infections. The effective absorption of these bacilli by the body would be demonstrated by variations in the reaction.

Much and Meinecke have affirmed that the auxiliary personnel of consumptive hospitals, and of the annexed services, presents at the end

of a relatively short period modifications in the sense of an accentuation of the cutaneous reaction. According to these authors, this would depend on the mild but frequent bacillary doses to which one is exposed in these surroundings.

Redecke believes that the allergic modifications indicated may be accompanied by modifications in the local manifestations of the disease. From clinical observation, he believes that we can arrive at the conclusion that the zones of infiltration, frequently observed in the course of a recrudescence of tuberculous infection of the first or second stage, have often been stimulated in this recrudescence by an external superinfection. These zones of bacillary localization would be observed and would frequently become evident in persons (principally infants) in a state of repeated superinfection. Following several personal observations, he has come to the conclusion that this superinfection must be attributed less to a direct inoculation with germs than to a true tuberculin reaction, as it were, determined by the absorption of the toxins of dead bacilli. Cases which, according to the author, would be able to confirm this type of observation are not lacking in the literature. That of Langer is typical. It concerns an infant sick for a year with tuberculous pneumonia who, several years later, following an injection of tuberculin, presented at the seat of the lesion reactions with definite zones of infiltration.

According to certain authors, the observations collected would tend to prove that, in the secondary period (in the anatomical sense) of the tuberculous infection in the adult, there may be superinfections of exogenous origin that provoke the disease, either by direct localization of the germs in the tissues or, still more probably, by the action of the toxins absorbed at the place of the latent foci, an action comparable to that from tuberculin. According to this conception, the germs of external superinfection, instead of multiplying at the site of inoculation, would be killed and destroyed *in situ*, and would act indirectly by the action of the toxins liberated and absorbed.

The demonstration of an exogenous superinfection appears still more debatable in the case of tertiary pulmonary tuberculosis. According to Braeuning, an analogous condition would be met in many cases of acute pulmonary tuberculosis in the adult, wrongly attributed to the results of an influenzal attack that never existed; and these cases would find a better explanation, on the contrary, in a local tuberculin reaction in the sense of Meinecke. According to the author, one can call to the

support of this opinion certain experiments on animals. The acute reaction observed following a reinfection, which often leads to congestion and necrosis of the tissues, would be attributable to the harmful action in the animal of the tuberculous toxins liberated by the bacilli injected, proportionately to the doses employed (Selter).

The close relation generally recognized to exist between pneumonokoniosis and tuberculosis is cited by some writers as proof of exogenous reinfection, a reinfection favored by the modifications produced in the lung by pneumonokoniosis. It would seem in a general way that such is the truth in many cases. But what I am going to point out, as well as the recent observations of Camerata, Gye and Kettle, H. S. Willis, Gardner and Dworski, Landis, and P. Hailman, would tend to limit the application of this rule. According to clinical, anatomico-pathological and experimental observations cited by these authors, the result, —and it can even be proved,—is that pneumonokoniosis renders the lung less resistant to tuberculous infection. But the infection varies also according to the frequency of medical examinations, the strict selection of workers, the hygienic conditions of work, and the economic resources of employed patients, etc., factors that notably diminish the importance of infection.

In all my experience, I can recall only a single case in which exogenous superinfection could be called upon in a convincing manner to explain the origin of a pulmonary tuberculosis. It concerned an observation on a pneumothorax performed on a subject in 1914, who was considered cured in 1915 to the extent of allowing him to assume the hard task of primary school teacher. Ten years later this man presented serious and diffuse tuberculous lesions in the other lung (proved to be healthy at the time of the end of the cure-period) at the root of the hilum, following cohabitation for about a year with a parent affected with pulmonary tuberculosis. In my experience, one meets more frequently patients with tuberculosis considered cured for a long time (for more than ten years in eight cases observed by me), who, passing into infected surroundings, present a return of their old lesions with rapid progression (from eight to twelve months in the cases that I observed), and with nothing that could have been modified in the individual conditions.

If the observations cited, can, in their entirety, be adduced in favor of exogenous superinfection, they do not permit of the conclusion that this mechanism occurs frequently in practice, nor can a metastatic origin through the blood routes, due to a focus of organic tuberculosis,

be absolutely excluded in these cases. The migration of bacilli in the blood, through endogenous superinfection, was demonstrated in 1914 by L. Bernard, Debré and Baron. The recent publications on this subject confirm this possibility (Löwenstein, Tooru, Koizumi). Acute pulmonary tuberculosis in the adult may equally find its explanation in a septic state of the body.

The clinical observations in favor of the endogenous theory are, in my opinion, much more numerous and convincing. The appearance of a tuberculous focus, following excess and prolonged fatigue and the setting in evidence during the menstrual period (all external superinfection being excluded) of progressive pulmonary localizations, cannot be adduced in support of this view.

The following facts seem to me more conclusive: The possibility of individual reinfections demonstrated by numerous cases of lupus and the majority of cases of infection of the mucous membranes, etc.; the benign nature of scrofulous tuberculosis (Bazin) and some varieties of traumatic tuberculosis (anatomical tubercle, ulcerative forms of tuberculosis from inoculation, some rare forms of scrofuloderma, etc.); the rarity of tuberculosis in persons with scrofula of long standing, as shown by Marfan in 1886. Whatever the interpretation given to these manifestations, they always demonstrate a condition of resistance of the adult body against exogenous superinfection.

Again it is necessary to mention the sudden appearance of tuberculous symptoms in direct connection with benign injuries, the local reactivation of the tuberculous focus due to a disturbance of the powers of immunity of the affected cells (Bergmann), all exogenous infection being excluded as far as possible.

Then the undeniable aggravation of tuberculosis mortality, following epidemics of influenza and other diseases known to cause asthenia, and the rarity of pulmonary tuberculosis, early or late, in the cases of severe penetrating wounds of the chest in gassed soldiers, as the War has proved, must also be mentioned. With regard to wounds of the chest, writers are in accord. In so far as the cases of inhalation of toxic gases are concerned, if it appeared at the outset that there was no etiological relation between this inhalation and the appearance of new tuberculous lesions, further observations would tend to modify this view. Investigation in the dispensary and more recent information furnished by assisting associations would seem to demonstrate that there is a higher percentage of pulmonary tuberculosis following toxic inhalations. If this fact came to be confirmed, it would be necessary to establish its

mechanism (infection from the exterior, endogenous superinfection, or modification of the terrain?). It seems strange in every way that organs, modified so profoundly from the anatomical and functional viewpoint, as a consequence, in conditions of lessened resistance, present biological characteristics contrary to those usually observed against tuberculous infection. The statistical references are given by Calmette in his recent remarkable communication on the prophylactic protection of the newborn against tuberculosis by means of the vaccine *BCG*. So far as infancy is concerned, they have acquired a general value. The prophylactic protection of the newborn, even of those who have remained for a certain time in contact with bacillus-carriers, represents a positive proof of the possibility of defense against external infection, and confirms the fact that the protection acquired under determined conditions should constitute the principal defense to tuberculous infection in infants as well as adults.

Finally, there is the demonstration of clinical forms of pulmonary tuberculosis which may evidently be attributed to endogenous superinfection. This question, which is of great clinical interest, has long been the object of special studies on the part of our school. For the particular aims of the report of which I have charge, I limited myself to the examination of 186 cases (observed by me) in my own dispensary and military practice. These cases came from the midst of contaminated families, and the patients lived under defective social conditions that were beyond criticism. Their ages varied from 20 to 40 years, the period of observation varying from ten to twelve years.

In 85 per cent of the cases, the cutaneous reaction was positive. Renewing this test at different and remote periods, I observed frequent variations in its intensity without regard to the infectivity of the environment. The causes of these variations are not always biological. A uniform and strict technique and the employment of a single type of tuberculin reduce them in an obvious manner.

In the first survey, carried through to the end, I was able to demonstrate old pulmonary tuberculosis, in a condition of clinical latency in the sense of Burnand, in 52 per cent of the cases. In 36 per cent of the cases, the long period of observation allowed me to observe the appearance of progressive lesions. The clinical forms disclosed may be grouped as follows:

1: Disseminated pleurocortical lesions, generally characterized by local progression in stages.

2: Foci of pleurocortical consolidation. These are localized principally in the supraspinous and subspinous regions, preferably on the right side, and possess the same progressive characteristics as the preceding symptoms.

3: Subclavicular consolidations of the interstitial type, located principally in the midst of this region.

4: Disseminated apical and subapical foci of the broncho-alveolar type, with protean and varying symptoms according to the severity of the cases, the duration of the symptoms, etc.

These signs are of great practical value because early diagnosis makes possible a true systematic prophylaxis of the severe forms of tuberculosis. Presenting uniform clinical characteristics, these lesions should be considered, as we shall see, as the expression of an endogenous infection, representing either a local recrudescence or, more often, a metastatic diffusion, whatever the route followed by the metastases. This view is shared by Alessandrini of Rome, who, in some interesting radiological investigations, pursued with the view of discovering the primary focus in the lung of the adult, demonstrated the relative frequency of apical and subapical foci, differentiated radiologically from the primary foci of childhood. These foci are, according to him, the sign of a beginning infection at adult age, through secondary diffusion from the hilum toward the apex along the peribronchial lymphatics.

Anatomically, my hypothesis finds numerous confirmatory facts.

I have already recalled that the primary focus is extinguished in exceptional cases, and that it may be lighted up again locally to a certain extent with the participation of some or all of its elements. These recrudescences (which represent the constant starting point, so to say, of the pulmonary metastases as well as those in other organs under all the circumstances that concur to create an asthenic state) can, in favorable conditions, be demonstrated to an equal extent by radiographic negatives taken in series.

In the opinion of anatomists, the primary lesion generally has a predilection for the cortical tissue of the subpleural region, and establishes itself most frequently in the right lung, and by predilection in the superior and anterior part of the upper lobe, and in the postero-inferior part of the lower lobe. These incontestable preferences of localization allow the supposition that the tubercle bacilli, after having passed the epithelial bronchial and alveolar epithelium in any manner whatsoever, are aspirated into the lymphatics by the negative pressure of the pleural space and thus carried away to a site underneath the

pleura. It is the same route which, in the same conditions and under the influence of the same factors, the particles of atmospheric dust passively follow in the lung. As counter-proof, this course may be interrupted whenever these forces directed toward the pleura are artificially abolished (artificial pneumothorax).

The biological and anatomical circumstances of the localization and the activity and recrudescence of the primary focus explain, in my opinion, the forms enumerated as categories *1* and *2* above. These relapses result from all those causes that determine in general the return and diffusion of tuberculosis in the human body. The groups under *3* and *4* should be considered as the leading expressions of an endogenous superinfection, to the extent that the metastatic symptoms of the reactivated primary focus (especially in the lymphatic portion) may be considered as reactivation and diffuse spread, starting from the cicatricial remains of the primary lesion. It is not possible to differentiate the two modalities clinically. They are combined and superimposed one upon the other. All writers who have applied themselves to the question are of this opinion (L. Bernard, Rist, etc.). The fact that the hilum and perihilar foci are often quiescent renders the appreciation of this subject more difficult. The foci can rarely be discovered by stethoscopic examination, because they are almost always deep. For evident physical reasons, they disclose their presence only when they approach the periphery (apices). In so far as the initial diffusion of the pathological process and the predilection of the primary lesions, anatomically secondary, for the apical and subapical regions are concerned, I come back to the anatomical and physiological facts and the local predispositions already cited.

I should, however, remark that the clinical categories which I distinguish relate, in practice, to ulcerative pulmonary tuberculosis through numerous forms of transition, and that the diverse categories, in certain conditions, cover all the progressive phases up to true pulmonary tuberculosis.

To the group of clinical symptoms of endogenous superinfection equally belongs the clinical phenomenon described by L. Bernard, and defined by the author as "upper lobitis."

This phenomenon, in my experience, is not so rare as is believed. It relates, in the majority of cases, to the forerunners of tuberculosis having passed through various phases and stages. *Lobitis* is considered, in the majority of cases, as the expression of an awakening of apical

lesions,—the residual primary lesions, which, being reactivated, resume their progressive march, though limited in their centrifugal development by a fissural reaction that may easily be discerned.

Among the clinical indications in favor of endogenous superinfection, one should still recall, in my opinion, the appearance of foci of tuberculosis on the side opposite the lesion in the course of pneumothorax (as much through awakening of old foci as through aspiration of infectious material coming from the compressed lung) and the complications in the neighborhood of the pneumothorax (especially the pleurisy). Competent writers, such as L. Bernard, Rist and Maingot, consider that the progressive recent hilum tuberculosis sometimes observed on the opposite side at the beginning of a pneumothorax is an argument of almost experimental value in favor of an exogenous superinfection. If this mechanism of production cannot be excluded in the cases of recent hilum tuberculosis in connection with pneumothorax, I believe, nevertheless, that it is debatable in all the other cases, because it is impossible to distinguish clinically whether the hilum localization is the expression of a bacillemia, an infection or the reactivation of old lesions.

In the cases observed by me, reactivation was brought about by all the causes of asthenia known for the adult, especially by pregnancy and lactation, by acute infections of the relapsing rheumatoid type, by influenza, appendicitis, septic cutaneous affections (well described in Italy by Campani and Grossi), and frequently by the social state of the patient (one of the predominant factors in the clinical antecedents of human tuberculosis). Very often, however, it is not possible to discover the determining factor.

From a critical examination of the facts presented, the following conclusions may be drawn:

We possess numerous clinical observations in favor of the endogenous origin of pulmonary tuberculosis in the adult. The foci are originated either by the reactivation of one or all of the elements of the old primary lesions or by the metastatic diffusion of germs coming from them.

It is, however, not possible to determine which of the two modalities is the most frequent in practice. The possibility of symptoms of pulmonary tuberculosis in the adult through exogenous superinfection is, however, clinically established. Materials hitherto gathered in favor of this hypothesis are nevertheless rare and limited, and tend to make one believe that this mechanism is not frequent in the adult. Exogenous superinfection may be mani-

fested either by localization of the germs absorbed into the pulmonary tissue, or indirectly by the toxic action developed by the tuberculous substances, which are absorbed but killed at the time of their entrance. Clinically, it is not possible to differentiate the two categories of cases.

Statistical Results

The material at our disposal is copious but not always convincing. One must not forget that the statistics have been gathered at different periods of time, and under different conditions, and by methods and criteria lacking in uniformity. So many different factors conduce to the breaking out of pulmonary tuberculosis in the adult that it becomes difficult to reach an exact evaluation as to the origin of the disease, even while studying ethnological groupings that are comparable with one another. Our judgment is rendered still more uncertain by other elements, of which the most important are the feeble infectivity of tuberculosis and the long time that elapses in the adult between the infection and the clinical manifestation of the active disease.

The diminution in the mortality from tuberculosis, the progress of which has been more rapid where the antituberculosis movement is best organized and most intensive (Denmark, United States, England), cannot be attributed only to the decrease in the chances for infection. This seems to be a question of a general phenomenon, which is observed equally in countries where the fight against the disease is insufficient. The causes of this decrease are many. They cannot be attributed by preference to one or the other factor. Emerson has shown this for the United States, which, by virtue of its resources, organization and methods, is at the head of civilized peoples in the fight against tuberculosis. The fact is not excluded that the measures adopted to trace and eliminate the direct sources of infection (examination of sputum, compulsory reporting, protection from sputum, isolation of outspoken cases of tuberculosis, pasteurization of milk, destruction of flies and prohibition of the common use of utensils, etc.) have contributed to reduce morbidity from tuberculosis at even adult age; but one should not disregard the importance of all the other social, economic and educational factors.

It is admitted by the majority of writers that military life, in the régime of the permanent army, is an important factor in the propagation of tuberculous infection, either through the promiscuity of the soldiers in the barracks or, as we have seen, by the movements of invalided patients who lead to rural contamination. The question has

been the object of recent very careful statistical investigations on the part of A. Jeandedier. This author brought out the fact that, so far as the army is concerned, one cannot assign a notable importance to infection in the spread of tuberculosis, whether because it is not possible to show an evident relation between the annual development of pulmonary tuberculosis and the number of tuberculosis patients eliminated to the board of revision (tuberculosis endemicity always being inversely proportional to the elimination of the suspects and those incapacitated from the army), or because the variations of pulmonary tuberculosis in the army correspond approximately to the variations of the disease in civil life.

The opinion, sponsored by Hillenberg and other writers, that war-time tuberculosis is a demonstrative argument in favor of exogenous superinfection, because many soldiers, incorporated as healthy, thereafter became tuberculous, does not correspond in a general way to reality. As a general opinion, war-time tuberculosis is due less to presence at the front than to a multiplicity of causes (fatigue, mental and physical tension in the soldier and the civil population, high cost of living, privations, insufficient nourishment, gathering in masses of the soldiers in the barracks, crowding in the cities, the concentration camps for prisoners, remoteness of sanitary assistance, intense industrialization, etc.). These causes in their entirety represent enervating elements of the first order, which are likely to facilitate the exaltation of an attenuated tuberculosis and the reactivation of latent forms (Ilvento, Ronzoni, Sforza, Ulrici, Hayek, Schröder, A. Engel, Miller, Knud, Hart, etc.). This conviction is confirmed by the following facts: In the armies, where sorting was possible and was carried on with all desired strictness, war-time tuberculosis presented, if one can say it, percentages corresponding to those of peace times. Its epidemiological spread corresponded in the combatant army to analogous phenomena observed in the nation; the increase of war-time mortality from tuberculosis, observed among combatant peoples principally during the latter period, did not extend to the years which followed peace, as it would have been logical to observe if the breaking out of the pulmonary tuberculosis had been connected with direct infection.

In this respect, certain authors have remarked that the diminution in the number of tuberculosis patients after the war should be attributed to the fact that the mortality from tuberculosis was more intense and concentrated during the war, and that this fact should influence

the general mortality for a certain time. Nevertheless, the remark may be made that the diminution in tuberculosis is continuing, and is becoming more marked, and that it appears as a general phenomenon also in countries that are put to the most critical test. The slight oscillations observed in different countries and for different ages may be explained by special local causes (influenza, for example).

The increase in the morbidity and mortality from tuberculosis in direct relation to urban and family crowding is considered by certain authors as an index of the multiplication of the dangers of infection. The phenomenon cannot, however, be interpreted in so simple a manner. In Milan, for example, before 1890, the proportion of deaths from pulmonary tuberculosis reached the figure of about 30 per 10,000, while, in 1908, the proportion fell to 21 per 10,000, although the density of the population had increased. This diminution should be attributed first and foremost to municipal improvements. But, while tuberculosis in the cities was decreasing, it was increasing in the country, paralleling the great industrial development; and it spread into communities hitherto relatively slightly attacked. We recall analogous information in the statistics of other countries. When, on the contrary, a city is exceptionally composed of isolated dwellings (as, for example, in Sao Paulo), one observes a very low mortality from tuberculosis (Bertarelli).

Most particularly, as concerns habitations, the observations of dispensary physicians confirm the fact that overpopulated lodgings favor the infection in city patients under their control. I recall the information given by Ilvento for the dispensary of the city of Genoa, information relative to the families of 2,706 tuberculous persons for a period of eight years (1910–1918): "Twenty-five per cent of the families examined were crowded together in a single locality. Sixty-six per cent of the patients shared their beds with other members of the family." These conditions correspond, in a general way, with the statement of a higher percentage in the mortality from tuberculosis. In Milan, this fact appears clearly from the statistics of P. Ferrari. But, from these facts and similar information, one should not immediately conclude that family crowding absolutely favors infection and creates tuberculosis in the adult. The statistics that I have analyzed indicate that the highest percentage of mortality and morbidity corresponds not only to the densest quarters of the city but also to the poorest.

The data that I cite, very interesting though they may be, have only an indirect value for the purpose of our thesis.

We shall come to more exact conclusions through the study of tuberculous infection in surroundings where the infecting tuberculous person finds himself in intimate contact with the healthy adult or one considered as such.

The first fact to determine is as follows: Are the morbidity and mortality from tuberculosis more frequent in surroundings where phthisical persons live? A decisive contribution to this problem could be adduced by dispensary physicians, who are in the best position to study the family collectively. The recent statistics of Braeuning would demonstrate that, in surroundings where there are phthisical persons, pulmonary tuberculosis is more frequently acquired. For Stettin for 1919–1921, this frequency was six times as great as for the rest of the civil population (from 5.4 to 32.5). Samson in his investigations arrived at similar conclusions (35.5 and 19.2). This accords with the results of my own experience in the dispensaries. In the families assisted by the dispensary which I direct, pulmonary tuberculosis in adult age is more frequent than in the urban population in general.

In these cases, can the appearance of the disease be considered as the result of the multiple contagion which accompanies it? Information furnished by Braeuning seems equally favorable to the idea of infection. The increase of tuberculosis in the families of phthisical persons is correlated with the prolongation of the life of the patient or the brevity of time after his death: 1.4 per cent of the new cases of pulmonary tuberculosis were observed by the author in the first two years after death, and 0.2 per cent from the third to the fifth year afterward.

But neither these statements nor their critical examination, in my opinion, permit us to conclude immediately that pulmonary tuberculosis is due more to infection than to predisposition. Various considerations require that we exercise caution in the evaluation of the preceding figures. If, for example, one separates the observations of Braeuning into cases coming from hygienic surroundings and patients living under bad conditions, 1.3 per cent of cases of the first group are obtained and 4.9 per cent of the second. I obtained similar results among my dispensary patients. These facts should keep us from drawing conclusions too hastily from tuberculosis rates in poor families and those suffering from bad hygienic and social conditions,—conclusions in favor of contagion as a factor in pulmonary tuberculosis in the adult would be too hasty.

These limitations become still more necessary when we compare the

information given by L. Denoyelle last year in his interesting thesis inspired by L. Bernard. In a minute investigation on the origin of 300 cases of pulmonary tuberculosis at adult age, the author observed that, in 26 per cent of the cases, the infection could be attributed with certainty to early life, and was presumed to be such in 41 per cent of the cases. Only in 6 per cent (perhaps in 13 per cent) of the cases could it be considered as connected with superinfection. The information adduced by Hillenberg from the study of the circumstances of infection and the antecedents of 259 tuberculous persons over 14 years of age confirms the rarity of late infection.

In summary, it is possible to conclude from these observations that the mortality and morbidity from pulmonary tuberculosis are higher in surroundings where phthisical persons live than in noninfected surroundings. However, in citing this phenomenon, one should bear in mind not only the great possibility of infection but equally other factors which notably reduce its practical importance (bad hygienic and social conditions).

The statistics of Turban on the spread of pulmonary tuberculosis among the auxiliary personnel of the hospitals have long been known, These statistics would tend to demonstrate that the personnel of the hospitals, who are particularly exposed to exogenous superinfection, do not exceed the average in morbidity from tuberculosis. In the same way as Ritter, in the course of twenty-three years of sanatorium work, Braeuning, in ten years, did not observe new cases of pulmonary tuberculosis among his personnel. Ulrici, in ten years, was able to admit, in three cases only, the possibility of pulmonary tuberculosis of external origin among his personnel.

These findings should prove favorable to the hypothesis of endogenous superinfection. Some authors, however, believe that the fact can be explained rather by the circumstance that the personnel is selected carefully at the time of engagement, and is rigorously supervised during service, and that it is a question of the personnel's practising the rules of personal prophylaxis. The recent statistics of Kirchner on tuberculous infection among the doctors and attendants of 549 institutions (public and private hospitals, clinics and sanatoria) would be in favor of this reservation.

Among physicians and students attached to hospitals, the author has observed 1.36 per cent of tuberculosis patients; in the sanatoria, 1.89 per cent; in the university clinics, 2.42 per cent. The mortality from

tuberculosis was 1.44 per cent among the attendants, and 0.77 per cent among the physicians.

The recent observations of Hammel and Müller, while arguing in favor of the possibility of exogenous superinfection, limit its importance. Hammel found an annual morbidity of 0.44 per cent among the auxiliary personnel, in the proportion of 0.68 per cent for the general hospitals and 1.58 per cent for the hospitals with wards for the tuberculous. A. Müller points out that attendants with latent pulmonary lesions become active with less frequency in the general services than in the services for the tuberculous; that is, 0.35 per cent as against 2.6 per cent.

Conjugal infection is considered by investigators as an experimental terrain, so to say, for the solution of the problem. To come down to concrete facts, it is a question of living in the same house with a tuberculous person and living with him in the intimacy of marriage. If, as has been seen, living together can present a relative possibility of contamination, conjugal life constitutes a probability, marked not by the special nature of the relations between the spouses, but by the serious potentialities of the contacts (principally by the buccal and respiratory routes), multiplied by the relations of every moment and by the difficulty of prophylaxis often being rendered valueless by the instincts of affection.

In conjugal tuberculosis, the intensity, multiplicity, and duration of the contact are realized to the maximum. The proportion of the possibilities of repeated and abundant exogenous reinfection, with which the healthy married person contends, is infinitely greater than that of the generality of adults. The statistical data cited by the authors on this question are discordant and often contradictory. From the 3 per cent of M. Fishberg, one comes to the quadrupled values indicated by A. Minning, and the conclusion of Wurd, that the majority of persons married to those with phthisis present sooner or later symptoms and indications of pulmonary tuberculosis. It is important, however, to remark that these statistics come from various periods of time, countries and social environments.

The examination of the most recent statistics, collected according to more uniform methods, permits us to arrive at clear and relatively consistent conclusions. Arnould was able to show, through statistics extending from 1874 to 1924, and including 53,069 cases of conjugal tuberculosis, with tuberculosis in both spouses in 4,472 cases, that the morbidity from tuberculosis in the spouses averages about 10 per cent,

while it does not exceed 5 per cent in the urban population for the ages from 20 to 50. The frequency of conjugal tuberculosis, therefore, would not, according to these investigations, be proportional to the importance of the possibilities of infection. The fact acquires greater importance when one bears in mind that many of the statistics presented by the author come from dispensaries, while the statistics of the other group are furnished by the aggregate of social life. If one interprets these findings by comparing the patients of the dispensaries and the poor population of the cities or of corresponding quarters, the percentage of mortality from tuberculosis as against that from conjugal tuberculosis is, in my opinion, still less than the values given by Arnould (about 8 per cent in the section assisted by the dispensary directed by me, a dense and populous section).

Denoyelle likewise found only 36 cases of conjugal tuberculosis in 167 contaminated families, the infection being certain in only 7.1 per cent of the cases. The recent statistics of F. B. Hermann are in accord with these conclusions. In only 4.3 per cent of the cases (270 families) was the author able to collect data in favor of an exogenous origin of the infection; in 85.9 per cent of the cases, this eventuality could be excluded. There is occasion to remark that in the author's statistics the morbidity among women was three times as great as that of men. Finally, in 432 families, in which one of the spouses presented bacillus-carrying pulmonary tuberculous lesions, Tecon was able to exclude all infection from the other spouse in 57 per cent of the cases, while the infection among the children was impressive, as much from the viewpoint of frequency as that of gravity.

In the statistics cited, it is a question, then, of differences too limited and disproportionate to the possibilities of infection. Their analysis allows of the conclusion that conjugal tuberculosis, in the sense of an exogenous superinfection between spouses, cannot be denied statistically, but that, despite the favorable conditions for infection, these cases are disproportionately few in number, if one considers the fact that the proportion of the morbidity from tuberculosis does not greatly exceed that of the other groups and that the difference between the two groups tends to diminish as soon as one considers similar groupings.

CONCLUSIONS

1. In the adult, it would seem that a relatively recent infection cannot be considered as responsible for the appearance of the clinical symptoms of tuberculosis, save when it takes place in virgin soil for the bacilli, of which condition instances are rare in our civilized life. In the latter instance, as in the case of individuals coming from unaffected peoples, the tuberculous infection begins and progresses with the characteristics of a primary infection.

2. Clinical study and pathological anatomy show that, in actual life, the lesions following primary infection are often quite far from being strictly latent, and that, in quite a few cases, tuberculosis in the adult is, more or less, a late and brisk manifestation of a preëxisting infection, contracted most often in early life.

3. The progressive tuberculosis of the adult, which results from a latent tuberculosis (principally of the lung), should be considered as the expression of superinfection. This superinfection may have its origin equally in the reactivation of old remains of lesions as through an external infection.

4. Endogenous superinfection may be considered as predominant in the majority of cases of extrapulmonary tuberculosis, through metastases coming from old reactivated foci. For pulmonary tuberculosis, experimental, anatomical and clinical observations, as well as statistical facts, allow the conclusion that endogenous superinfection should be considered as the predominant, if not the absolute, element of the disease, as much through the local reactivation of old lesions as by the mobilization and spread of the germs contained in the lesions themselves.

5. If exogenous superinfection cannot be admitted to be the rule in the pathogenesis of pulmonary tuberculous infection in the adult, it cannot be excluded. It is not possible to decide how greatly its importance should be evaluated. According to experiment and clinical observations, the importance of massive infection in the adult should not be exaggerated. Superinfections of small and repeated doses appear to play a more active rôle. The infection in the adult may act in a direct manner by transporting germs that penetrate and localize themselves in the tissues, and in an indirect manner by the toxic action developed by the bacilli, killed and reabsorbed at the site of penetration, and acting on the preëxisting lesions like a stimulant, analogous to tuberculin. This eventuality is perhaps preponderant.

6. Superinfection, whatever its mechanism, finds a modified allergic terrain in the adult, an expression of the preceding infection, which is revealed by a greater resistance to the germs and by a greater sensitiveness to their toxin. In the adult, the allergic state is variable, unstable and subject to diverse influences, of which many are known and the others are less well determined. Fully recognizing that the allergic state is the equilibrium which, in relation to the number of infective bacilli, governs the progress of the superinfection, one should not completely forget, in the pathogenesis of pulmonary tuberculosis in the adult, the clinical findings based on the general and local predisposition of the terrain.

7. The practical fundamental rules that one can draw from this knowledge are the following:

a. Prophylaxis against tuberculous infection should be applied principally to the defense of childhood, because this is the most vulnerable age to the infection.

b. Prophylactic protection and vaccination of infancy against tuberculosis, even while we await their results, are to be considered as the most efficacious practical means against tuberculous infection in the adult.

c. The modern prophylactic defense should take account equally of endogenous superinfections as well as those coming through contagion.

d. In the actual state of our knowledge, no restriction can be admitted as to the possibility of infection at adult age. One should, therefore, maintain and apply with conviction and rigor all the defensive measures proposed and recognized to be efficacious to conquer and wipe out the infection.

e. The early recognition of tuberculous infection in the adult, through diagnostic institutions and dispensaries, is considered as one of the most important points of defense, as much for the prophylaxis of the serious forms of tuberculosis (principally pulmonary) as an element in the control and diminution of the infection.

EXOGENOUS REINFECTION IN PULMONARY TUBERCULOSIS[1]

LAWRASON BROWN

In any discussion of "adult infection," it seems very necessary to define the terms used. *Infection* may mean simply an implantation of the tubercle bacillus in the human body, but I take it that in this Conference it includes also infection that has advanced to actual clinical disease. The term *adult* also requires definition. If we divide the age-period of infection into childhood and adult periods, it seems to me that the age of puberty would be a fair dividing line, that is, about the age of fifteen years. Accordingly, in discussing "adult infection," it is necessary to consider only infection after the age of fifteen years. It seems hardly necessary to mention bovine infection in this discussion on account of its rarity in adult life, though Much holds that infection of an adult with the bovine bacillus is no more difficult than with the human strain. As pulmonary tuberculosis is the cause of death in over 87 per cent of all the deaths due to tuberculosis in the United States, and as pulmonary tuberculosis is in the vast majority of cases the type of tuberculosis found in adults, it seems hardly necessary to consider in this discussion any other form.

1. PRIMARY INFECTION

From the study of the tuberculin tests infection has been assumed to be almost universal in most civilized countries. At what age does this occur? In certain European cities the figures would suggest that such a condition is to be found about or shortly after puberty. In many American cities and communities, about 50 per cent of positive cases at puberty would be more accurate. At the Trudeau Sanatorium, where for years we used the intracutaneous tuberculin test upon every patient admitted to the institution, there occurred but two instances among

[1] Presented in the *Discussion* of *The Part Played by Contagion in Tuberculosis among Adults*, at the Fifth Conference of the International Union Against Tuberculosis, Washington, D. C., September 30, 1926.

some thousand cases in which the test was negative, though at times we had to employ rather large doses of tuberculin. Of these patients we found that 10 to 15 per cent had no discoverable tuberculosis. If we might draw an inference from this latter group it would appear that practically 100 per cent were or had been infected. The ages of these patients varied, of course, but the majority were in the third decade. Naegeli's pathological studies also showed that by the fourteenth year 50 per cent have tuberculous changes, while at the nineteenth year 96 per cent have been infected. If now we accept a statement that only 50 per cent of individuals are infected at puberty, and 100 per cent before the age of thirty, we are forced to the conclusion that about 50 per cent are infected after puberty or during early adult life. Such infection, however, does not imply clinical disease nor even the actual presence of infection, but it does suggest that possibilities of infection and implantation of tubercle bacilli come to practically every city-dweller before the end of the third decade. It follows, of course, that most of us have repeated infections, occurring from time to time, but in the majority of us they play little part in the disease except possibly along the line of immunity. Of course in certain rare individuals among civilized communities, and in many individuals among races not subjected previously to tuberculous infection, such infection during adult life may often be quickly followed by acute tuberculosis. It is also possible that repeated intracutaneous tests with increasing doses of tuberculin may considerably increase the number of those reacting at puberty, and we may find that only 25 to 30 per cent are infected after puberty. These conclusions, are, of course, based upon the assumption that tuberculin skin sensitiveness is very rarely lost.

If we accept the belief that early in the third decade the vast majority of dwellers in civilized countries have had at least one infection, and probably some have had many, the question arises at once: Does the pulmonary tuberculosis that develops most frequently in the third decade come from the primary early infection, that is, does it arise from endogenous reinfection or can it be attributed to an exogenous reinfection? Few to-day would have the temerity to deny that tubercle bacilli can continue to live for years in the body, hidden, for example, in some lymph node, and later break out to bring about adult pulmonary tuberculosis. Not a few, however, do affirm that once infected the human organism is rarely if ever again subjected to such a dose of tubercle bacilli from without that it cannot resist. This they hold is particularly

true in adult life. Few, I believe, will deny that such adult infection takes place, but many question whether adult exogenous reinfection is ever severe enough in civilized countries to bring about clinical disease. This is indeed a very vital and practical problem, worthy of all the study that we can give it. If, after the age of puberty, for instance, we find that effectual infection, infection capable of bringing about clinical disease, never takes place, we can modify our attack upon the disease in such a way that we can bend our efforts to prevent infection before puberty, and afterward to forestall unnecessarily debilitating conditions. Furthermore, it seems highly probable to me that if such conditions are found to be true, we shall not be long in discovering a method by which we shall be enabled to discover at or before puberty those who in future life are likely to develop pulmonary tuberculosis.

2. SECONDARY INFECTION (REINFECTION, SUPERINFECTION)

In order to facilitate discussion it might be well to consider the problem of adult reinfection from different viewpoints; for instance, (1) the evidence adduced from experimental data, (2) the evidence from clinical investigation, and (3) the evidence from roentgenological study. It must not be imagined for a moment that the evidence from any of these points will more than indicate the line along which probably profitable work may be pursued.

The Evidence Adduced from Experimental Data

Experimental data, as usual, speak for and against effectual adult infection. If we divide all animals into two groups, resistant and susceptible, man, Cobbett holds, falls into the resistant division. It may be fair, as he states, to compare him only with animals falling into the same group. Fortunately, we have in this group the bovines, animals already subjected to much experimentation in tuberculosis. Here, of course, we have incontrovertible evidence that adult infection does occur. Calves successfully immunized with human tubercle bacilli resist infection under natural conditions until they approach adult age, and then reinfection with bovine tubercle bacilli may occur. As we have no evidence to show that the human type is ever transformed into the bovine bacillus, it seems highly probable that reinfection from without has taken place. Many cattle slaughtered after reacting to tuberculin reveal evidence only of primary infection though subjected

to continuous exposure. On the other hand, Theobald Smith states that cows with tuberculous lymph nodes may show reinfection of the lungs. It is of interest to note that small doses produce only small or localized lesions, but that the animals vary much in their reaction to the same dose.

Many experimental workers hold that exogenous reinfection is most unlikely, for they find it very difficult to reinfect tuberculous animals with tuberculosis except with massive doses. But these workers usually experiment upon animals with advancing tuberculosis, and attempt to compare such results with reinfection in man in whom the previous infection had occurred many years previously. Whether or not this can safely be done is at present difficult to determine.

If tuberculosis runs, when tending toward arrest, a course in the guinea pig similar to that in man, it would appear that the natural span of life of the guinea pig (about three years in captivity) is insufficient in many cases to allow of arrest of the disease. Hence it would appear that any conclusions drawn from such animals must be more or less inaccurate. But, on the other hand, Baldwin and Gardner have found that guinea pigs may lose the tuberculin test after about fifty-four weeks, (which they consider evidence of arrest of their tuberculosis), but regain it after reinfection. It is of interest to note that they question whether it is ever lost in man, but Krause and Austrian have each reported cases in which apparently it was lost in man.

Cobbett has found that when he infected guinea pigs by ingestion the first lesions were found in the cervical lymph nodes, and that the lungs were involved only when generalized tuberculosis was present. After infection by inhalation the first lesions occurred in the lungs, and the mesenteric and ileocolic lymph nodes were never involved, the cervical lymph nodes being infected only after involvement of the spleen.

That fewer tubercle bacilli are required to infect animals by inhalation than by any of the other natural routes is now accepted. Gardner has shown that a strain of tubercle bacilli, which fails to produce pulmonary tuberculosis in guinea pigs when inoculated by the subcutaneous or intravenous route, may possibly, in rare instances, bring about pulmonary infection when sprayed into the upper respiratory tract. In rabbits the lungs are readily infected by subcutaneous or intravenous inoculation, but inhalation experiments are still lacking. If we can accept Findel's work, it would appear probable that doses many thousand times as large (some would even have it a million times) are required to

infect guinea pigs when the tubercle bacilli are given by way of the alimentary tract as when given by inhalation. The mouth and fauces would appear to be more grossly infected by the feeding than by the inhalation experiments. Selter has been able to infect guinea pigs by inhalation with doses as small as five bacilli. Only droplets under 15 micra are said to penetrate into the finer bronchioles, and such droplets contain very few tubercle bacilli; some, indeed, say only one. In a study of 1,400 cases with reference to the occurrence of human and bovine tubercle bacilli, it was found that 50 per cent of tuberculosis of the abdominal lymph nodes, 41 per cent of the cervical lymph nodes, 23 per cent of generalized tuberculosis, and no cases of pulmonary tuberculosis in children were due to the bovine tubercle bacillus, although the infection was almost certainly due to the ingestion of infected milk. Either the lung must have greater immunity to the bovine tubercle bacillus or infection of the lung must in the vast majority of cases be by inhalation. It is possible, of course, that after puberty, the lung may react differently to the tubercle bacillus.

The study of the pathological changes in the lungs of guinea pigs after direct superinfection by inhalation, and after extension of the process to the lungs from a primary focus elsewhere, is of considerable interest. The tubercles following inhalation appear first beneath the pleura, while those from autogenous metastatic reinfection are found at any point in the lung (Gardner). In this connection it is of great interest to recall that pulmonary tuberculosis can be discovered by the usual physical exploratory methods only when it is situated near the surface of the lung.

It is impossible in this discussion even to mention the names of the numerous experimenters. The subject has been reviewed recently by Baldwin and Gardner and, like many others, they found that guinea pigs show a marked resistance to reinfection which, however, did not prevent reinfection if a sufficiently large dose was used.

There is also some experimental data upon infection in man. The tuberculin known as *BE*, and used very extensively in 1901, was shown later to contain living tubercle bacilli, but so far as I am aware no superinfection from its use was ever reported. Both bovine and human tubercle bacilli have been inoculated into man with apparently little or no harm. Baumgarten, F. Klemperer, Garnault, Calmette and others inoculated bovine, and A. Moeller and Webb and Gilbert, human bacilli. The last observers produced a positive Pirquet test and an enlarged lymph node in a child with fewer than ten living bacilli.

The Evidence from Clinical Investigation

Search for exposure to open pulmonary tuberculosis is still emphasized by many writers on the diagnosis of pulmonary tuberculosis. Any evidence to be drawn from it is, of course, very inconclusive. However this may be, Dr. Warren and I have made a study of the history of infection in 1,000 cases at Trudeau Sanatorium. We found that the data obtained from many patients were necessarily inaccurate for childhood exposure, and often inexact for adult exposure. This question must be worked out in communities where access can be had to the homes. Much work has been done alone this line.

It has been stated that the parent is twice as dangerous for the offspring as the tuberculous husband or wife is for the well consort (Pearson). Pollak and again Bergman found that the danger of infection greatly decreased after the age of four.

According to Hess, deaths from tuberculosis increase markedly at puberty in both sexes, which, if due to infection, must be ascribed to a continuous infection or reinfection, which he does not accept but cannot disprove. It might be advanced as evidence of a change or decrease of immunity at puberty which favors reimplantation of tubercle bacilli from without. Newsholme states that figures from hospitals for the tuberculous, often quoted as showing the infrequency of infection, when carefully analyzed may bespeak exogenous reinfection, and do not prove that reinfection is impossible. It must not be forgotten that domestic and hospital conditions are very different from each other; and that reinfection may occur in one and not in the other. The high incidence of pulmonary tuberculosis among religious orders has been put forward as evidence of adult infection (Cornet, etc.).

In a study of 252 cases of rural tuberculosis Ward attributed 40 per cent to immediate infection (reinfection?), 19 per cent to remote and 10 per cent to doubtful contact, and 31 per cent to no discoverable contact. In 96 tuberculous children 74 per cent were immediate, 2 per cent remote, 1 per cent doubtful, and 23 per cent negative contacts. In 102 negative nontuberculous control cases Ward found 5 per cent exposed to immediate, 7 per cent to remote, 6 per cent to doubtful, and 82 per cent to no discoverable contact. A study of 77 tuberculous soldiers showed 5 per cent immediate, 26 per cent remote, 2 per cent doubtful and 67 per cent no discoverable exposure.

It is difficult in considering adult infection to explain why marital

infection is not more common. These cases should be divided into two groups: (1) those in which one consort contracts the disease after marriage, and (2) those in which one consort is frankly tuberculous at the time of marriage. It is highly probable that in the former case infection of the other spouse may be very slight at first, and in most cases stimulate the resistance so usually present in the dwellers in civilized communities. In the second group we find two classes: (1) those who marry patients who have had pulmonary tuberculosis, possibly without recognition, and have increased resistance, and (2) those who have but slight resistance. If members of the latter unfortunately marry patients whose sputum is highly infectious, reinfection, clinical disease and death may follow. Here belong the cases mentioned by Parkes Weber and others, in which a tuberculous husband loses one or more wives (even four) and yet remains alive. Attention has, I believe, already been called to the fact that death from tuberculosis of the healthy consort almost certainly does not follow in all instances of marital infection. A percentage, larger or smaller, must either recover from their tuberculosis, or at least live long enough to die from other causes. This is very likely to follow in cases in which the reinfection takes place in more resistant soil, a resistance brought about by previous infection. As a matter of fact, more deaths occur among the consorts of tuberculous partners than occur among the general population, suggesting, of course, that adult infection, though slight, does occur in such cases.

Objections can be advanced to almost any clinical evidence that can be adduced. For instance, Franz tested 1,002 recruits for the Austrian army with tuberculin, using doses of 0.001 and 0.003 O.T. While 68 per cent of those from localities where tuberculosis was prevalent and 38 per cent from healthier localities reacted, after seven years it was found that of the 64 who had developed pulmonary tuberculosis only 46 had reacted originally to tuberculin. To-day we would not accept such a dose of tuberculin as necessarily sufficient to bring about a reaction in a tuberculous person, but the results, so far as they go, suggest exogenous infection even if they are certainly not conclusive.

Few would have the temerity to advance the view that a relapse in an arrested case was due to an exogenous reinfection. In nearly all such cases the fresh outbreak is found to be in the neighborhood of the old lesion. In an occasional case it does occur in another part of the lung or, indeed, on the other side. In autopsies in other diseases than tuberculosis it has been found by Naegeli and others that, with advanc-

ing age, the number of cases with evidence of previous tuberculosis steadily increases. Here again, while such findings suggest exogenous reinfection, we are left in uncertainty.

The Evidence from Roentgenological Data

The X-ray evidence bearing upon this point is very interesting. The disease was excluded after a prolonged study in 412 patients sent to the Trudeau Sanatorium with a diagnosis of pulmonary tuberculosis. These cases have been followed from two to ten years, and only 3 of them have developed clinical manifestations of the disease. Of these, 2 had a definite tuberculous focus in the body at the time of study. The patients whose disease progressed into more advanced stages have nearly all had a well-defined parenchymatous lesion in the lung. These statements hold true for all patients, no matter at what age they came under observation, but it must be noted that children are not admitted to the institution. Such observations would suggest that if a parenchymatous lesion had not been acquired at the time of study, there was little likelihood of its future occurrence. If we might push our inference a bit further we might assume that, if a parenchymatous lesion had not been acquired by the age of twenty, there was small likelihood of its occurrence at a later date.

It is now widely accepted that the primary infection in man is usually in the lung, occurring as it does in 80 to 90 per cent of all cases. The work of Küss, of H. Albrecht, of Ghon, of Opie, has all shown this. The idea occurs at once to us all: Cannot the pulmonary tuberculosis of adults arise from this primary infection? Mr. Sampson and I have examined a large number of patients with minimal pulmonary tuberculosis and with evidence of a previous primary complex. In most instances we were able to show that the adult pulmonary tuberculosis arose elsewhere, often in the opposite lung. As a matter of fact, in only two or three cases was there even a suggestion that the adult pulmonary tuberculosis arose in the neighborhood of the primary infection.

It has not yet been determined in what proportion of cases adult pulmonary tuberculosis arises from a secondary pulmonary focus, preexisting possibly from childhood or from a date shortly after puberty (15 to 20 years). Until the use of roentgenograms became more or less general, problems such as this were impossible not only of solution but also of attack. Work has been begun along this line, notably by Chad-

wick of Massachusetts and Rathbun of New York. The Massachusetts Department of Public Health two years ago began the examination of the underweight school children in the state (under the direction of Dr. Chadwick). A physical examination is made of all those 10 per cent or more underweight, of the contact cases, and of any special children who are in poor condition and who do not come within the two former classes. All undergo a cutaneous tuberculin test, and those who react are X-rayed. During the first year 10,098 were examined and 2,650 reacted to tuberculin. Of these, 26 had a definite parenchymatous X-ray lesion and 485 (5.1 per cent) had "hilum" tuberculosis, while 1,257 were classified as "suspicious." If we accept as having positive pulmonary tuberculosis those with the hilum changes, we have about 5.3 per cent of positive cases. These children were in the first to the eighth grade, ranging in age from six or seven to fourteen or fifteen years. During the second year 29,171 children were examined, and 0.12 per cent were found with pulmonary tuberculosis and 3.8 per cent with hilum changes. Of the 35 cases of pulmonary tuberculosis, 7 were males and 35 were females. Chadwick in his sanatorium work finds that three to five times as many girls as boys have positive sputum in cases in which the ages range from three to seventeen.

Rathbun examined 538 children between the ages of six and twelve, referred to the clinic on account of poor general condition. Of these, 8 (1.4 per cent) had parenchymatous pulmonary involvement, 2 (0.4 per cent) pleurisy with effusion, 6 (1 per cent) bone tuberculosis, 3 (0.5 per cent) lymph-node tuberculosis, 27 (5 per cent) were suspects, and 73 (14 per cent) were held for further observation. The pulmonary lesions found in these younger children were not, as a rule, as extensive as those occurring in the high-school children. Apparently no tuberculin tests were done on any of these children. The difference between these findings and those obtained by Chadwick in Massachusetts are very marked, but Chadwick selected from the underweight group his cases for radiological study by the use of tuberculin, subjecting all those who reacted positively to the X-ray. Rathbun's figures are so much higher than Chadwick's that the suggestion occurs at once that their classification or terms are differently applied. Rathbun does not employ the term "hilum" tuberculosis, while Chadwick makes extensive use of it. It is also highly probable that every suspicious case in Chautauqua County passes under Rathbun's observation. If we combine the figures of Chadwick with those of Rathbun, we find that 43 (0.14 per

cent) cases had a parenchymatous pulmonary lesion, for the larger numbers of Chadwick outweigh those of Rathbun. In 142 children a definite history of contact was obtained by Rathbun, and of these, 12 (8 per cent) had definite parenchymatous lesions, 19 (13 per cent) were suspects, 69 (49 per cent) were kept under observation and 42 (30 per cent) were negative.

Rathbun has made a study of 1,000 high-school (including junior high school) students, ranging in age from thirteen and fourteen to sixteen and seventeen, in Chautauqua County (population about 125,000) in the western part of New York State. Practically every student in six high schools was examined. Of these students those with previous or present symptoms suggesting tuberculosis, those with a history of contact, however slight, and those with positive or suggestive physical findings were X-rayed. The results were that 13 had healed or active parenchymatous pulmonary lesions, 3 had healed tuberculosis of bones or joints, 2 old cervical lymph-node tuberculosis, 1 had pleurisy with effusion, 17 were held as suspects, 66 were kept under observation, chiefly on account of a history of contact or of poor general condition, and 889 were negative. The morbidity among the athletes was greater than in any other class.

The freshman class at Smith College, about 650 students, were examined by Chadwick, and one active and two chronic cases of pulmonary tuberculosis were discovered, while about 10 per cent of the others had primary lesions or hilum lymph nodes undergoing calcification.

DISCUSSION

There are three camps in regard to this problem: *1.* Those who believe all tuberculous infection arises from childhood infection, that is, from endogenous reinfection at any time in later life. *2.* Those who feel that many or indeed most cases of pulmonary tuberculosis in adult life are due to infection from without, that is, an exogenous reinfection from inhalation, and in most cases in civilized countries upon a more or less sensitized soil. *3.* Those who seek a golden mean, who hold that both endogenous and exogenous reinfection can occur, but that possibly endogenous reinfection is the more common and that exogenous reinfection rarely takes place after the twenty-fifth year.

To attempt to trace the tubercle bacillus from its entry into the body until it produces pulmonary tuberculosis in the adult is more difficult

than many realize. For example, let us suppose an infant of three or four years of age has become infected, is possibly under par for a time but then recovers, and has a vigorous childhood and youth. At 26 or 27 years of age the individual develops pulmonary tuberculosis. Some would assert that in about 80 per cent of such instances the reinfection which has brought about the pulmonary tuberculosis has come from the infantile infection. When pressed to state how this comes about they advance different theories. Some hold that the tubercle bacilli rest encapsulated in one or more lymph nodes for twenty-two or twenty-three years. During the interplay of increased and lessened resistance, indicated, some think, through the decreased and increased response to the intracutaneous test, the wall of the lymph node weakens, and finally possibly, as the allergy is again increased, ruptures, and the tubercle bacilli and disintegrating tissue-products gain entrance to the general or lymphatic circulation and are carried to the lungs. Here some are fixed, and develop more or less rapidly to bring about adult pulmonary tuberculosis from endogenous reinfection or superinfection. They offer few explanations of why in early pulmonary tuberculosis so few tubercle bacilli after endogenous reimplantation become virulent and why, if many tubercle bacilli are discharged into the circulation, so many pass into the lungs and are never again heard from. Some would vary this course by stating that reinfections from without may act like large doses of tuberculin and bring about congestion surrounding the sites of previous but nonclinical tuberculosis. Such congestion they hold would more likely flush out tubercle bacilli from these foci, and such tubercle bacilli, gaining entrance into the blood-stream, would become fixed in the lungs where they first come in contact with capillaries. A bronchogenic spread from the original focus can, of course, take place.

Gardner infected guinea pigs by inhalation with a culture of tubercle bacilli nearly avirulent. He then, at varying intervals, subjected the animals to inhalations of dust, and found that up to five months after the primary inhalation the dust apparently caused a spread of the tuberculosis from the infected bronchial lymph nodes to the lungs. Gardner interpreted the pulmonary tuberculosis as due to an endogenous reinfection from the lymphatic involvement, but has not yet, though he plans to do so, excluded the possibility that the pulmonary tuberculosis was due to a few tubercle bacilli lying dormant since the primary inhalation in some of the lymph masses at the divisions of the bronchi and vessels in the lungs.

Many affirm that tuberculin sensitiveness once acquired is never lost, and that the allergic state when once developed continues through life. Austrian and Krause, however, report cases, in which, after the child recovered from its tuberculosis, it failed to react to Pirquet tuberculin tests, and Baldwin and Gardner found this true in some guinea pigs tested intracutaneously. There are, so far as I am aware, no records of a series of cases tested by the skin (intracutaneous) tuberculin reaction before puberty and found positive and retested after puberty, although Krause has reported the case of a boy who in childhood was for years excessively sensitive to tuberculin while suffering from multiple tuberculosis, and who, since his clinical cure, has failed to react to Pirquet tests given annually for nine successive years (from fourteen to twenty-two years of age). It is possible that a certain number might fail to react to a second test performed after puberty. Such individuals might constitute a considerable number of those who develop pulmonary tuberculosis in or after the third decade, but this, or course, is highly hypothetical. It is of interest to note, in passing, that cattle which have made complete recovery from the previous human infection no longer react to tuberculin.

Those who favor exogenous reinfection as the cause of adult pulmonary tuberculosis also face many difficulties. If we again assume a similar hypothetical case, like the one mentioned above, we see a long period existing between the primary infection and the development of clinical pulmonary tuberculosis. During this period they would have us believe that the infected individual gradually loses more or less of his allergy and his acquired resistance, which are not necessarily parallel. Allergy is probably rarely lost entirely, if we can assume the intracutaneous tuberculin reaction as an indication of its presence. It is highly probable that all persons living in civilized communities rarely pass through a year without taking in some tubercle bacilli from the outside. What becomes of these tubercle bacilli? Many are no doubt destroyed before they can gain an effectual implantation; but others, they say, do gain a foothold, probably most usually in the allergic lung, and struggle for existence until some event, untoward for the individual, so reduces his powers of resistance that the bacilli are enabled to make some headway toward producing a lesion which approaches the threshhold of clinical manifestation. In all probability numerous and repeated debilitating circumstances are necessary for the development of this reinfection into clinical disease. It is also possible that the subliminal lesion may become

a point of lessened resistance, and so aid in other reinfections in or about the same area.

It is an interesting observation that so many primary infections occurring in early life leave some trace in the lungs. This, some aver, is upheld by the work of Küss, Ghon, Ranke, Opie and others. From the experimental work of Gardner and others it would appear that the lungs are more easily infected by inhalation than by other means, that is, fewer tubercle bacilli are required to produce infection; and tubercle bacilli, which may fail to produce pulmonary tuberculosis in guinea pigs when inoculated by subcutaneous or intravenous routes, readily bring about pulmonary lesions when sprayed into the upper respiratory tract. Such observations the proponents of exogenous reinfection urge in favor of the possibility of adult reinfection affecting the lungs. To carry the argument further, they ask: Why should the lungs be so often the seat of a primary infection in early life when clinical pulmonary tuberculosis is far less common, and be so rarely the seat of exogenous reinfection in later life when pulmonary tuberculosis is by far the most common type of the disease? Some go so far as to assume that the infection of the lung at all ages is most probably due to direct infection brought about by inhalation. Some experimental work of Krause and Willis would suggest that tubercle bacilli introduced into the body by inoculation quickly find their way to the lungs and bronchial lymph nodes. This would suggest that infection by deglutition, a most common form in early life, may be responsible for the pulmonary disease in a few cases.

The observers of this group ask upon what grounds the holders of the endogenous reinfection theory base their assumption that, after years of quiescence in an old encapsulated tubercle, any large quantity of tubercle bacilli are poured into the circulation in such a manner as to produce a very localized pulmonary tuberculosis. Why, they continue, may not the body be equally or indeed more resistant to this strain of tubercle bacillus than to another? Roemer, however, could discover no such difference in guinea pigs. They are not unaware of the generalized or localized acute tuberculosis which follows the rupture of a tuberculous lymph node into a vessel or duct. If exogenous reinfection does not occur after puberty, what, if any, danger of infection is there for those who react to tuberculin?

Opportunities for infection, many hold, are very common,—so common that some state that other factors must be present to bring about endogenous or exogenous reinfection. That tubercle bacilli may remain for

a long time in the tissues without producing gross or microscopic changes has been widely accepted but it seems to me on insufficient grounds. Loomis found that 26 per cent of those dying from other diseases than tuberculosis had tubercle bacilli in apparently normal tissue and Calmette thinks this figure too low.

It is of interest to note that the tubercle bacilli found in or near the old foci have been only assumed, not proved, to have been there for years. Such an assumption is probably correct in the case of the calcareous nodule, but even here Fishberg states that the fibrous encapsulating capsule is rarely perfect. He presents this fact as an explanation of how endogenous reinfection can take place from such a lesion. However, it is entirely possible that such lesions may form *loci minoris resistentiae*, and thus bring about the deposition of some of the tubercle bacilli from the numeous exogenous tubercle bacilli that gain entrance into the lungs from time to time. In this way tubercle bacilli in these locations may be new arrivals from fresh strains of tubercle bacilli and not from the original strain that brought about the formation of the lesion.

Much assumes that the primary infection of childhood brings about immunity and that constant new reinfections strengthen this immunity. Such an admission would lead us to infer that reinfection which increases immunity might in some cases lead also to an advancing reinfection. Much states later on that the tuberculous person does destroy all tubercle bacilli coming from without, thus preventing reinfection, and many from his own foci. Such statements are of course highly hypothetical.

From what data we have it would seem that adult infection does occur, and that it occurs much more frequently than many have supposed. The important problem, however, is: Does this infection, occurring after the age of fifteen years, ever result in adult pulmonary tuberculosis, and, if it does, how frequent is it? Whether or not the tubercle bacillus is ubiquitous, many believe that to-day adults are constantly being exposed if they dwell in congested communities. Some of these implantations up to the end of the third decade may be primary infections, which the natural resistance, acquired possibly through heredity, enables the individual to resist, though it renders him allergic or hypersensitive to later infection, which, as I have said, is more or less continuously taking place. Others of these implantations result in reinfections, and may add to the acquired or natural immunity already present, or, if they occur at a time when the bodily forces are at a low ebb, they may produce a definite focus of disease, which for a longer or shorter time may

remain undiscoverable by clinical means. The occurrence of debilitating circumstances may finally bring this adult infection, or more often reinfection, into activity, and clinical disease thus result. It is not likely that reinfection is followed at once by clinical disease.

The period during which reinfection takes place may extend from infancy to middle life, but exogenous reinfection probably occurs most frequently from the fourth to the twentieth years. Roentgenological studies indicate that by the tenth to the twelfth year many children have definite parenchymatous pulmonary involvement. Evidence is still lacking to prove that these are the subjects that will develop adult pulmonary tuberculosis from the fifteenth to the twenty-fifth year, but such an inference is strongly suggested. It may be that future study will show that these cases comprise many of those referred to in an earlier section of this paper as having peritruncal pulmonary lesions, which, as we know, do follow in some instances of healed adult pulmonary tuberculosis lesions which apparently afford their bearer almost complete immunity to a future parenchymatous pulmonary tuberculosis. If this is proved to be true by future work, then reinfection from puberty to the twentieth year may yet be found to be the most frequent cause of adult pulmonary tuberculosis. I am convinced that a certain percentage, somewhere between 20 and 40 per cent of adult pulmonary tuberculosis, is due to infection after puberty. I do not mean to imply that endogenous reinfection does not frequently take place, but I should like to protest against the assumption that it has been proved to be the most frequent manner of production of pulmonary tuberculosis or, indeed, that it is proved at all.

THE PART PLAYED BY CONTAGION IN TUBERCULOSIS AMONG ADULTS[1]

STEPHEN J. MAHER[2]

In the hope of adding a little to our knowledge of the difficult subject proposed for our discussion to-day, I have endeavored to open-mindedly study fresh histories of 200 patients at present under treatment in the State of Connecticut. This I have done with the hearty coöperation of the medical staffs of Connecticut's three sanatoria for adult consumptives. The only conditions observed in selecting the 200 cases were that the patients should have sputum positive for tubercle bacilli, and should be sufficiently intelligent to be interested in giving truthful answers to the questions put to them. Ninety-three of the patients are at Laurel Heights Sanatorium in Shelton, 44 are at Cedar Crest Sanatorium in Hartford, and 53 of the patients are at Uncas-on-Thames Sanatorium in Norwich. In order to make the number an even 200, I added the histories of 10 active cases from my private practice.

"Contagion in adult tuberculosis" is of two kinds: (1) the contagion that is received in childhood and that develops into adult tuberculosis and (2) the contagion that is received after childhood and that develops into adult tuberculosis. In my study of 200 cases of adult tuberculosis, the histories of cases nos. 4, 18, 25, 26, 45, 73, 93, 125, 160, 178 and 189 indicate the possibility or even the likelihood that the present tuberculosis is the result of childhood contagion. In cases nos. 16, 40, 41, 64, 86, 88, 91, 111, 116, 121 and 166, the histories indicate the possibility that the present tuberculosis is the result of contagion received during adult life. In cases nos. 14 and 53 the histories strongly indicate the probability that the present adult tuberculosis is the result of contagion received in adult life.

In all others of the 200 histories there was nothing that gave ground for suspecting that contagion, childhood contagion or adult contagion,

[1] Presented in the Discussion of the clinical subject, *The Part Played by Contagion in Tuberculosis among Adults*, at the Fifth Conference of The International Union Against Tuberculosis, Washington, D. C., September 30, 1926.

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had anything to do with causing the present tuberculosis. In a case, in which several members of a family who had drunk freely of tuberculous milk in childhood and who had been living apart for many years after childhood and who in distant cities or states had developed pulmonary tuberculosis, I have ascribed the adult pulmonary tuberculosis to tuberculous milk, and not to contagion.

If in these 200 cases of proved adult tuberculosis, not more than 11 cases could have been caused by contagion in childhood, and if not more than 11 cases give a history of possible contagion in adult life, and only two cases give a history of probable contagion in adult life, where did the tuberculosis of these 200 cases come from? A difficult question. A question that demands a carefully studied answer. Here is the material for study offered by an exhaustive examination of the patients and their histories:

Causes of Adult Tuberculosis Suggested by Histories of 200 Cases

	Cases
Contagion in childhood (possibly)	11
Contagion in adult life (possibly)	11
Contagion in adult life (probably)	2
Tuberculous milk	13
Nontuberculous lung disease	85
Severe skin disease	45
Severe abdominal disease	21
Severe throat disease	38
Dusty occupation	100
Noxious fumes	11
Bad working conditions	6

The possible causes that the histories of these 200 cases suggest are given in the above table. Of course, it must be realized that more than one cause is often suggesed in a single history. For instance, the history of case 32 reveals the fact that the patient worked several years in an atmosphere of dust, and that when he was 18 years old he suffered from severe pneumonia. Case 132 gives a history of severe scarlet fever, repeated furunculosis and pneumonia. Case 105 drank no milk, knew of no possible contact, but had tonsillectomy at 17 and appendicitis during pregnancy, and appendicectomy fifteen months after her baby was born. The combination in the same case of dusty occupation and pneumonia, pleurisy or tonsillitis was frequent.

As it is important to know my reasons for deciding that contagion may

have had to do with the causing of tuberculosis in a given case, I will attempt to briefly state them:

Adults possibly infected in childhood

Case 4: Married male, aged 23. Possible childhood contagion from tuberculous mother. First symptoms at 21 years. Much calcification and fibrosis of both lungs. Severe attack of mumps at 17 years. Shortly before tuberculosis appeared, patient developed a great crop of boils on arms and on abdominal wall. No adult contagion.

Case 18: Single female, aged 25. Possible childhood contagion from tuberculous mother. In 1918, severe influenza kept her in bed two weeks and incapacitated her for 4 months. After that, in good health until Spring of 1925. No adult contagion.

Case 25: Single female, aged 20. Possible childhood contagion from fat father who always coughed, but was not supposed to be tuberculous. No adult contagion.

Case 26: Single female, aged 18. Sister of Case 25. Possible childhood contagion from fat father who always coughed but was not supposed to be tuberculous. No adult contagion.

Case 45: Single male, aged 21. Always a heavy drinker of mixed unpasteurized milk. His mother died of tuberculosis when he was four years of age. He was sent to live with aunt as soon as mother's tuberculosis was diagnosed. Appendicitis and pleurisy a year ago.

Case 73: Single male, aged 25. Possible childhood contagion from tuberculous father and mother and sister. Patient, syphiltic, ascribes his sickness to his many years of work in the heat and wetness of his factory steam-rooms. No adult contagion.

Case 93: Single female, aged 18. Possible childhood contagion from tuberculous sisters. Clinically her sickness seemed to be related to an acrid purulent uterine discharge that still resists treatment. No adult contagion.

Case 125: Divorced male, aged 54. Possible childhood contagion from father who was considered tuberculous when patient was 4 years old; but who was cured by outdoor life. No adult contagion.

Case 160: Married female, aged 44. Possible childhood contagion from tuberculous father and mother and sister. No adult contagion. Severe whooping-cough at 18, severe pleurisy at 22, and severe attack of furunculosis at 7 years of age.

Case 178: Single male, aged 19. Possible childhood contagion from tuberculous mother, but he was taken away from his mother when he was one year old, four years before she showed symptoms of tuberculosis. His boyhood and

adolescent years were years of great hardship and of insufficient food. No adult contagion.

Case 189: Single male, aged 25. Possible childhood contagion from father; but he and his father worked in the same dust-laden air of a Canadian cotton mill. Others of family, mother, two brothers and one sister, who did not work in cotton mill, are quite well. No adult contagion.

Adults possibly infected after childhood

Case 16: Single female, aged 24. Possible adult contagion from tuberculous mother. But patient worked in a room, the air of which was full of cotton dust, and she had repeated attacks of winter tonsillitis.

Case 40: Single male, aged 25. Possible adult contagion from tuberculous elder brother.

Case 41: Married female, aged 36. Possible adult contagion from husband, who always had a chronic cough but was not considered tuberculous.

Case 64: Married female, aged 38. Possible adult contagion. A trained nurse. She nursed a tuberculous sister for six months. That was six years before her own first symptoms, which appeared after a severe attack of influenza.

Case 86: Married male, aged 21. Possible adult contagion. A sister died of pulmonary tuberculosis two years ago. Although there had been no contact for a couple of years before her death, they had grown up together, and for some months after she began to cough they had eaten at the same table. On the other hand, he had worked nearly three years in an atmosphere of dust,—cotton dust and emery dust.

Case 88: Single female, aged 32. Possible adult contagion from tuberculous fiancé to whom patient was engaged for four years before his death. However, she worked six years in the thick dust of a cotton mill. Also, she had severe attack of pleurisy when a child.

Case 91: Single female, aged 32. Possible adult contagion from tuberculous brother; but during childhood she was in hospital four and a half months for some mysterious abdominal inflammation and while in the hospital had a severe attack of diphtheria, and another of mumps. Also, she had severe pneumonia when two and a half years old.

Case 111: Married female, aged 42. Possible adult contagion. Nursed supposedly tuberculous husband during two years of empyema. Husband now well for many years.

Case 116: Married female, aged 30. Possible adult contagion from first of two husbands who died of tuberculosis in 1918. Patient dates beginning of her sickness to severe abdominal operation for removal of gall-stones and appendix. Also, after her second marriage, she worked for a year as polisher in a spoon factory.

Case 121: Single male, aged 21. Possible adult contagion from tuberculous elder brother, but patient himself was a metal grinder in dusty factory.

Case 166: Married female, aged 34. Possible adult contagion from tuberculous husband, who died four years ago. Patient insists that as soon as his cough began, tubercle bacilli were discovered, and he was sent away. However, they had lived together nine years. Patient worked many years before and after marriage in factory inhaling continually hard dust of dried glue.

Adults probably infected after childhood

Case 14: Married female, aged 32. Probable adult contagion from mother. Patient had severe smallpox in childhood, and had tonsils removed when 17 years old.

Case 53: Single female, aged 28. Probable adult contagion. She chummed with and nursed her tuberculous brother for several years. She had, as a first symptom, a sudden haemotpysis, a week before brother's death from meningitis. Her family ascribed her sickness to her violent efforts to reduce her weight.

Milk cases

How about tuberculous milk? Nine-tenths of the patients had not been milk drinkers at any time; that is, they never drank milk except in tea or coffee. I made an effort to learn whether in infancy they had been breast-fed or bottle-fed. Only half a dozen admitted that they had not been nursed by their mothers, but the answers were so often merely guesses that I could lay little stress on the point.

However, in 14 of the 200 cases, there was a history of long-continued drinking of tuberculous or suspicious milk. In one case of spinal and pulmonary tuberculosis, in which the patient said he had always drunk enormous quantities of milk, it developed on investigation that he had drunk only pasteurized milk.

These milk cases require explanation. Of course, in none of them can it be proved that the drinking of tuberculous milk caused the disease. My reasons for saying that their histories suggest milk as the causative agent are as follows:

Case 8: Married female, aged 25. In her childhood home in Poland, she drank much admittedly tuberculous milk. In this country she had typhoid fever in 1918 and appendicectomy in 1923. First symptoms of tuberculosis in 1925.

Case 10: Single male, aged 26. Always drank much unpasteurized milk from the one untested cow that the family owned. Eight years after separating from relatives and leaving the family farm, patient and a brother and a sister were stricken with pulmonary tuberculosis.

Case 34: Single male, aged 22. In childhood and youth, drank much nonpasteurized milk from the cow that the family kept. However, went from school to "dusty and smelly job in a rubber factory." Had malignant mumps and severe tonsillitis before leaving school. His rheumatic father, still on the farm, developed tuberculosis a month ago, three and a half years after beginning of patient's tuberculosis.

Case 45: Described under possible childhood contagion.

Case 99: Married female, aged 57. Drank much milk from two cows that her family kept on farm in Russia. One of these cows had mammary sores; but patient's two brothers and two sisters, who also drank of this tuberculous milk, are living and well.

Case 104: Single female, aged 22. Drank much mixed nonpasteurized city milk. Father died of spinal and pulmonary tuberculosis, but patient had had nothing to do with parent for many years before his sickness.

Case 107: Married female, aged 28. Drank much mixed nonpasteurized city milk; but had severe gonorrhoea within the year preceding her present sickness.

Case 127: Single male, aged 21. He and young sister, the only children in the family, always drank much mixed nonpasteurized city milk. Sister is dead of tuberculosis at 16 years of age. Patient had appendicitis since the development of his pulmonary tuberculosis.

Case 136: Married male, aged 39. Bottle-fed. Drank much mixed unpasteurized milk. Patient ascribes his sickness to severe "flu" 18 months ago, while engaged in dusty work on roads.

Case 138: Widower, male, aged 41. Drank much mixed uncertified unpasteurized milk here and in Poland; but he worked 9 years in Poland and in this country at very dusty work as cabinet-maker.

Case 179: Married male, aged 32. Drank much mixed unbottled milk, but had tonsillitis every year until tuberculosis appeared. No tonsillitis since.

Case 188: Married female, aged 22. Insists that she was bottle-fed in infancy with mixed unpasteurized milk. Ascribes her sickness to colds caught at dances.

Case 194: Single male, aged 17 years. Always drank much nonpasteurized milk (6 glasses a day) from his father's untested Holstein cows. Had repeated winter tonsillitis. Tonsils and adenoids removed 3 years ago. No dust. No contact.

The nontuberculous pulmonary diseases include 37 cases of pneumonia, 22 cases of pleurisy, 9 cases of severe acute bronchitis, 13 cases of influenza, and 4 cases of asthma. The debatable group under this head is, of course, the acute bronchitis group. But in most of these cases appar-

ently healthy young women who had drank no milk, and who denied possible contacts, became overheated and chilled after dances, and suffered for a week from the ordinary symptoms of acute bronchitis. Soon after these symptoms cleared up, the patients began to suffer from malaise and loss of weight. Within a few weeks or months, tubercle bacilli were found in their sputum.

The 45 cases of severe skin disease were: erysipelas 3 cases, furunculosis 14, cold abscesses 2, pustular acne 15, severe scarlet fever 4, malignant measles 4, and smallpox 3.

An interesting observation on the relation between skin infections and pulmonary tuberculosis was made last year by A. Campani in *Presse Médicale, 1925, xxx, 482.* "He examined 300 tuberculous patients, and found that 72 had had furuncles and carbuncles, 21 phlegmons, 87 septic wounds, i.e., a total of 180 patients out of 300 with skin infections. The coincidence of infected skin and lung on the same side of the thorax was shown in 78 per cent of the cases." (*Notes On New Remedies,* December 1, 1925.)

I have not been able to find in my 200 cases nearly so large a proportion of skin infections as Campani, but the subject remains an interesting one.

The 21 cases of abdominal diseases were: appendicitis 12 cases, inflammation of kidney and bladder 3, of intestines 1, and of ovaries and tubes 1, protracted inflammation of bowels 1, severe jaundice 2, typhoid fever 2. The possibility of a poorly understood relationship between tuberculosis and appendicitis, gonorrhoea and typhoid fever has long been suggested by clinical experience.

The 38 cases of throat disease were 30 cases of severe or repeated tonsillitis and 8 cases of diphtheria. In 13 of the 30 tonsil cases tonsillectomy had been performed.

In the 100 cases of dusty occupation, the offending material was cotton dust in 21 instances, woolen dust in 4, metal dust (steel and brass) in 19, stone dust in 30, cloth dust in 5, wood dust in 10, silk-mill dust in 3, tobacco dust in 4, hard-rubber dust in 2, and saloon-sweeping dust and celluloid dust, 1 each. Some of the patients, as the table shows, had worked in more than one kind of dust.

The "noxious fumes" class include 3 cases of fumes from molten lead, 3 from hat-factory steam-rooms, one from acid fumes, one from gasoline fumes, two from lacquer fumes, and one from spelter fumes.

Under "bad working conditions" are included cases, in which apparently healthy patients, with no history of contact, or of drinking of tuberculous milk, or of dusty occupation, or of serious childhood sicknesses, have developed tuberculosis when working too many hours with inadequate food, sleep and sunlight.

Perhaps the most startling revelation of the histories of these 200 tuberculous patients is the finding that 100 had been engaged for long periods in dusty occupations, occupations in which they inhaled dust of one kind or another all day for long periods of time. Of course, the number of patients studied is too small to permit of dogmatic generalization on the relation of these various kinds of dust to the causation of tuberculosis.

The question of whether the long and continual inhalation of cotton dust in certain cotton mills is even a contributing cause of adult pulmonary tuberculosis, is probably an open one. I do not pretend to close it. Stone and metal dusts of various kinds have long been under indictment in many parts of the world as causes of consumption. It was to be expected that, in a prosperous manufacturing State like Connecticut, evidence in support of this indictment would easily be found. But it was not to be expected that in a group of 200 intelligent consumptives, at present under treatment, 100 of them would prove to have been employed for long periods in dusty occupations. And even less was it to be expected that 21 of these 100 would prove to have been workers in cotton dust.

Of course, if you believe that tubercle bacilli are omnipresent and unavoidable in civilized life, and that autopsies demonstrate the fact that at one time or another everybody becomes infected with tuberculosis, and that all adult tuberculosis is the result of contagion in adult life, you will not be greatly interested in the consideration of such occurrences in the previous history of a consumptive as his attacks of pneumonia, of furunculosis, or of appendicitis, or in questions as to whether he worked in stone dust, or metal dust, or cloth dust, or spent his days and parts of his nights in sweat-shops. You may, of course, admit that these various happenings in the life of an adult consumptive possibly had a mysterious effect in "reducing his resistance," but you will insist all the more loudly that it was "contagion and contagion only" that actually caused this adult consumptive's disease.

Your belief is plausible, but as reasons for calling to your attention

these various nontuberculous events in the histories of these 200 patients, I would ask you to remember:

1. Doctors and nurses of tuberculosis hospitals and sanatoria, who are continually exposed to contagion, seldom if ever contract tuberculosis at these institutions.

2. The wives and children of consumptive workers in stone or metal dust very seldom have tuberculosis.

3. If contagion causes all adult tuberculosis and all adults are potential victims of the disease, the disease would be claiming more and more victims every year, whereas as everybody knows the number of its victims is diminishing every year. This demurring argument was naïvely put by Leroy in *La Médecine Moderne, 1902, no. 15*, and it is quoted approvingly by Jaime Ferran, the well known Spanish authority:

> In Paris from 10,000 to 12,000 die every year from pulmonary tuberculosis. If we fix 5 years as the average clinical duration of the disease, it will be seen that there are now in Paris 50,000 persons who are every day disseminating myriads of tubercle bacilli into their environment everywhere throughout the capital of France. If there is really such a thing as contagion in pulmonary tuberculosis, it must be admitted that every one of these 50,000 consumptives in Paris infects in the course of a year at least a dozen of the people with whom he comes in contact. At this rate, there wlll be at the end of the year, more than 500,000 tuberculous inhabitants of Paris and at the end of the second year 5,000,000 tuberculous inhabitants of Paris. That is to say, that at the end of two years, the whole population of Paris will be tuberculous.

4. As to autopsy findings, many investigators, among them Cobbett, A. S. Griffith, F. Griffith of England and Weber of Germany, have found that the caseous material from many of these cases cannot produce tuberculosis in guinea-pigs. And, to quote Cobbett (*Causes of Tuberculosis, p. 71*):

> On the result of these investigations, then, one must freely admit that many of the lesions believed on anatomical grounds to be tuberculous, but which are found in persons who have died of other causes than tuberculosis, do not contain living, or at least virulent bacilli, and that therefore, there is no reason to believe that they can ever be reactivated.

5. To argue that pneumonia or other nontuberculous disease or condition may have direct connection with causing tuberculosis, seems like mental retrogression, and as ridiculous as advising an army equipped with

machine guns to try the muskets used in the Wilderness. Perhaps so; but in these late days many of the best minds engaged in the scientific study of tuberculosis question the fundamentalist doctrine that every case of tuberculosis is the result of contact with another case of tuberculosis. Certainly, in these late days our opportunities for prolonged intimate association with tuberculous adults have been markedly diminished. The antituberculosis campaign, with its sanatoria and its intensive educational and publicity propaganda, has brought to every school and home and factory so great a dread of the tubercle bacillus and of the tuberculous human being, that consumptives are glad to be segregated. And, more important still, the families and friends of consumptives, whether rich or poor, no longer hesitate to send their loved ones to sanatoria, or to take whatever precautions their doctors advise. The anomalous result is, that although the number of consumptives diminishes every year, the demand for admission to sanatoria increases every year. May not this lessening opportunity for contagion be the explanation of such findings as I report in my tables to-day? And may it not be that the reduction in the tuberculosis death-rate throughout the civilized world has been mainly on contact cases? And may it not be that the cases of tuberculosis at present resistant to the great guns of our educational army are these cases that develop in mysterious ways from irritation by nontuberculous dust, or from nontuberculous inflammations of the skin or mucous surfaces? May it not be?—but that is another story, a bacteriological story, the story of transmutation.

CONCLUSIONS

1. Of the 200 cases of adult tuberculosis studied for the preparation of this paper, the histories of hardly more than 5 per cent indicate that the disease could have been caused by contagion in childhood, and that in hardly more than 5 per cent could the disease have been caused by contagion in adult life, and that in not more than 1 per cent of the cases was there a strong probability that the disease was caused by contagion in adult life.

2. In 6.5 per cent of 200 cases of adult tuberculosis the histories indicated a possibility of infection from the drinking of tuberculous milk.

3. In 50 per cent of 200 cases of adult tuberculosis, the patients had been engaged for long periods in dusty occupations.

THE VARIABILITY OF LOCALIZATION OF TUBERCULOSIS IN THE ORGANS OF DIFFERENT ANIMALS[1]

III. THE IMPORTANCE OF THE GROWTH OF TUBERCLE BACILLI AS DETERMINED BY GASEOUS TENSION

H. J. CORPER, MAX B. LURIE AND NAO UYEI

In Studies I and II of this series (1) (2) on guinea pigs, rabbits, dogs and monkeys, in which the deposition of tubercle bacilli and the tuberculous involvement of the various organs, following the intravenous injection of tubercle bacilli, were presented, it was noted that, regardless of which of these four species of animals was being considered or of the total amount of tuberculosis found in the lungs after the intravenous inoculation of living tubercle bacilli, the individual tubercles in the lungs were always larger than those in any of the other organs of the same animal.

The rabbit develops massive disease of the lung after such intravenous inoculation, even though this organ is the site of the deposition of far fewer bacilli than are the liver or spleen. In the guinea pig the tuberculous involvement in the lung is greater than that in the liver during the first four weeks after intravenous infection, although the total amount of tuberculosis developed in the liver of the dog after the injection of moderate amounts of bacilli exceeds that in the lung, the individual pulmonary tubercles are much larger than those occurring in the liver of this animal and, if the infecting dose is small, the lung is the only organ that becomes involved. Although the spleen, liver and bone-marrow in the monkey are the sites of more tuberculous involvement, after intravenous inoculation, than the lungs, yet the size of the individual tubercles in the latter organs far exceeds that in all the other organs of the same animal, and pulmonary disease was never absent in the monkey, regardless of the size of the infecting injection, while the other organs often escaped macroscopic involvement. In the four species of animals mentioned, the lung occupies such a position of peculiar susceptiblity to tuberculosis after intravenous inoculation, that would seem to indicate that in this organ there exists a responsible factor differing from that present in the other organs.

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

In contrast to the lung, the liver occupies a position of resistance to tuberculosis, since in the liver of all the species studied more bacilli are deposited than in the lung. The liver of the rabbit fails to develop any appreciable involvement even after long periods of time, and during the first four weeks after intravenous inoculation the guinea pig's liver develops less involvement than does its lung. After the injection of small amounts of bacilli, the liver of the dog does not display any tuberculosis while the lung is regularly involved. Even the highly susceptible monkey occasionally presents no disease in the liver. The size of the individual tubercles in the liver of these four animal species tends to be smaller than those found in any other organ in the bodies of the same animals. Even though each of the four species seems to have an organic predilection, such as the rabbit's lung, the guinea pig's spleen, the dog's liver with moderate infecting doses, and the monkey's spleen, liver and bone-marrow, the peculiar opposite positions, as regards susceptibility of the lung and liver under certain conditions in all the species, points to a common instrumental factor in both organs.

The most apparent difference between these two organs, and one which might plausibly explain their opposite positions regarding susceptibility, would seem to be the differences in gases available for the respiration and growth of the tubercle bacilli. After intravenous injection tubercles in the lung develop in close proximity to the alveolar air, while those in the liver develop in close proximity to the hepatic sinusoids. The alveolar air has the highest oxygen tension and the lowest carbon-dioxide tension of any internal part of the body, while the liver sinusoids are bathed with a blood containing a preponderance of venous blood, and hence have a lower oxygen tension and a higher carbon-dioxide tension than the capillaries of any other organ. This difference in the gaseous environment of the tubercle bacilli deposited in these two organs is common to all the species studied.

In earlier investigations (3) the effects of different atmospheres of carbon dioxide in confined systems on the growth of tubercle bacilli *in vitro* were studied; and it was soon realized that the errors of such studies could only be remedied by using open systems and constant flows of gas (oxygen and carbon dioxide) mixtures. These investigations were well under way, when Novy and his coworkers (4) reported their studies on the same question. The method pursued in the following study has aimed at a reproduction of bodily conditions as nearly as this has been feasible *in vitro*. The principle of the method was to have a

constant flow of a given gaseous atmosphere pass over growing cultures of different strains of tubercle bacilli.

THE EFFECT OF DIFFERENT TENSIONS OF CARBON DIOXIDE ON THE GROWTH OF TUBERCLE BACILLI IN VITRO

Plan of experiment

The gas, containing approximately 21 per cent oxygen and various concentrations of carbon dioxide, was prepared in large gas reservoirs. The gas-mixture was regulated to constantly flow through jars containing cultures of tubercle bacilli. The growth of the bacilli was recorded weekly, and compared with the growth of control cultures exposed to a continual flow of atmospheric air under the same conditions of temperature and humidity.

The carbon dioxide used in this experiment was obtained in cylinders from the Bishop Babcock Co. of Manitou, Colorado. It contained from 94 to 97 per cent of carbon dioxide and 0.40 to 0.44 per cent of oxygen by analysis. Oxygen was obtained in cylinders from the Lennox Chemical Co., Cleveland, Ohio. It was guaranteed to contain no impurities. Upon analysis by the alkaline pyrogallol method it was found to be 100 per cent pure.

The gas-reservoir tank was constructed of galvanized-iron plate and its capacity was about 100 litres upon calibration. It consisted of an inner or upper cylinder sleeve fitting into an outer or lower container on a stand. The latter contained a water-seal, covered with a thin layer of albolene, so as to reduce to a minimum the absorption of the carbon dioxide by the water.

In order to prepare a gas containing 20.98 per cent oxygen and a definite concentration of carbon dioxide (for example, 3.63 per cent), the following equation was used for the purpose of calculating the amounts of air, carbon dioxide and oxygen to be introduced into the tank.

x = number of litres of 96 per cent CO_2 to be introduced.
y = number of litres of 100 per cent O_2 to be introduced.
75 = number of litres of air to be introduced.
0.03 = percentage of CO_2 found in the air.
0.44 = percentage of O_2 found in 96 per cent CO_2.

$$75 \times 0.03 + 96x = (75 + x + y)\ 3.63.$$
$$75 \times 20.98 + 100y = (75 + x + y)\ 20.98.$$

Solving for x and y:

$x = 2.954$ litres 96 per cent CO_2.

$y = 0.788$ litres 100 per cent O_2.

In actual practice these gases were first measured in a carboy of five or ten-gallon capacity over water, and expelled into the gas-tank by means of water-pressure. Then the volume of the mixture was made up to the required volume (78.74 litres in the above example) with compressed air.

Analysis of gases

Oxygen: The Hempel gas-burette and a double absorption pipette containing alkaline pyrogallol solution, made according to Benedict (*Carnegie Inst. of Wash. Pub., 166, 1912, p. 80*) were used in the analysis of oxygen.

Carbon dioxide: A forty per cent solution of potassium hydroxide was used in Hempel's absorption pipette. To minimize the error due to the reduction in vapor tension, the inside wall of the burette was kept moist by means of a few drops of distilled water.

The gas-reservoir tank containing a gas-mixture of desired composition is placed outside of the incubator room. The gas-tank was connected by means of lead tubing into a small gas bubbler (diagram 1, *B*), which contained a small amount of distilled water, and was used to gauge the speed of gas-flow regulated by closing or opening the gas cock (a_1) attached to the tank. From the gas-gauge the lead tubing ran to wash-bottle (*D*) containing distilled water, and thence to jar 1 (*E*) and jar 2 (*F*), containing culture-tubes of tubercle bacilli. From jar 2 the gas was led into a small bottle (*G*), containing a small amount of distilled water and thence was allowed to escape. Bottle *G* acted as a trap, so that no open communication existed with the outside air. All connections between glass parts or metal parts and the lead tubing were made with short pieces of heavy-walled rubber tubing, which were carefully paraffined to ensure against leakage.

Four types of tubercle bacilli, *Gluckson*, a virulent human strain, *Human*, an avirulent human strain, *Bovine Virulent*, a virulent bovine strain, and *Bovine D*, a relatively avirulent strain of bovine bacilli, were used throughout this investigation. Ten tubes, containing Petroff's medium, were seeded with each type of bacilli by the suspension method. The tubes were cotton-plugged, and placed in a large jar, which was covered with black paper and stoppered tightly with a rubber stopper, paraffined and connected to the tubing for gas exposure. The

growth of the bacilli was examined weekly by removing the tubes, and comparing them with the growth of the controls. The only difference between the control and experimental culture was that a current of ordinary air was passed through the jars containing the former instead of an artificial gas-mixture in the case of the latter. The same suspension was used for seeding the experimental and control tubes.

The analysis of the gas-mixture in the tank was made before the gas was used in the experiment. In actual practice, one tank was placed in its position outside the incubator and was not removed during the experiment, the gas used being replaced from day to day from another tank. The gas cock (a_1), after being connected to supply the gas to the

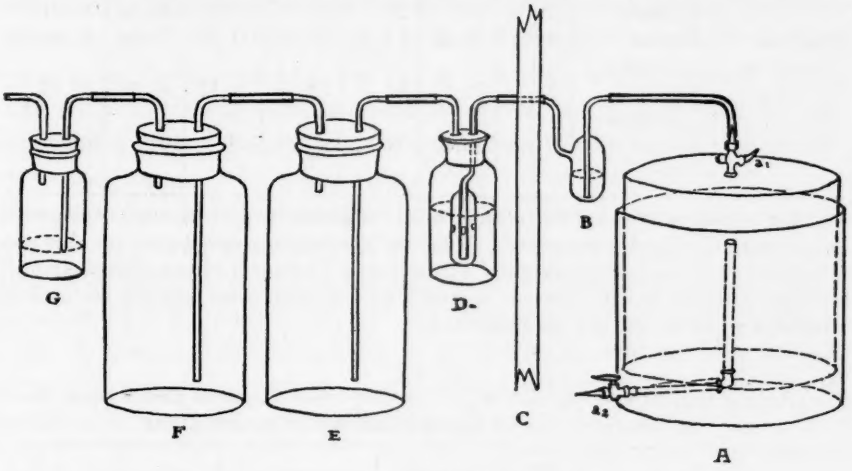


DIAGRAM 1
For description see text, p. 68

culture-tubes, was not disconnected, but the gas cock (a_2) was used for adding the new supply of gas, for about 25 to 35 litres of gas were used per day. The outflow gas was analyzed every morning.

In the carbon-dioxide experiments the oxygen concentration of the gas-mixtures was maintained at approximately that of atmospheric air (21 per cent) throughout, while the carbon dioxide was varied as follows: In series A, 3.5 per cent; series B, 7.3 per cent; series C, 14.5 per cent; series D, 36.3 per cent; series F, 54.5 and series E and G, 72.6 per cent.

No inhibitory effect of the carbon dioxide on the growth of tubercle bacilli was noted until the concentration reached 54.5 per cent of an atmosphere in Denver, the average atmospheric pressure in this locality

being about 628 mm. of mercury. On the contrary, with lower concentration of CO_2, about 14.5 per cent, tubercle bacilli seemed to grow slightly better than in atmospheric air.

TABLE 1

The growth of tubercle bacilli in vitro in 7.3 per cent carbon dioxide in Denver (equivalent to 6.0 per cent at sea-level) and approximately 21 per cent oxygen

	TUBERCLE BACILLI	ONE WEEK		TWO WEEKS		THREE WEEKS		FOUR WEEKS	
		Control	Gas culture	Control	Gas culture	Control	Gas culture	Control	Gas culture
Growth recorded on 10 different culture tubes	Gluckson	0*	0	21	11	31,32	11,22	41,32	21,22
	Human avirulent	0	11	61,42	31	72,33	21,52	73,34	32,43,34
	Bovine virulent	0	0	71,32	81	72,33	21,82	93,14	32,73
	Bovine D	0	0	31,72	21,82	42,63	103	104	104

* The amount of growth of the tubercle bacilli was graded from 0 = no appreciable growth to 4 = an excellent and heavy growth. If 2 of the 10 tubes had a one-plus growth, they were recorded as 21; if 3 had a four-plus and 7 a three-plus, as 73,34; or, if all had a four-plus growth they were recorded as 104. Absence of growth for any cause is not recorded unless all the tubes were negative; then it is designated as 0.

TABLE 2

The growth of tubercle bacilli in vitro in 72.6 per cent carbon dioxide in Denver (equivalent to 60 per cent at sea-level) and approximately 21 per cent oxygen

	TUBERCLE BACILLI	ONE WEEK		TWO WEEKS		THREE WEEKS		FOUR WEEKS		AFTER 2 WEEKS' EXPOSURE TO AIR
		Control	Gas culture	Control	Gas culture	Control	Gas culture	Control	Gas culture	
Growth recorded on 10 different culture-tubes	Gluckson	0*	0	91	21	41,62	81	42,63	21,72	
	Human avirulent	0	0	91	11	72,33	71,22	83,24	92,13	
	Bovine virulent	0	0	81,24	0	93	0	73,24	11	62
	Bovine D	0	0	91	0	72,33	0	83,24	0	71

* The amount of growth is graded as designated in the footnote to table 1.

In an atmosphere of 72.6 per cent carbon dioxide and 21 per cent oxygen, tubercle bacilli regularly show a distinct inhibition over those

grown in an atmosphere of 54.5 per cent carbon dioxide and 21 per cent oxygen. The growth records of series B and E alone are recorded in tables 1 and 2, since these will suffice to make clear the important points of this experiment. The daily record of analyses of the inflow and outflow gas from the jars will also not be given for obvious reasons.

No differences were noted in the effect of high carbon-dioxide tensions upon the growth of the different types of tubercle bacilli. As a whole, these findings agree with those recorded by Novy, except that an inhibitory effect of carbon dioxide on the growth of tubercle bacilli was noted in lower concentrations, which may be due to the difference in the method of the experiment. Novy and his associates used a closed system, and during the experiment there developed a pronounced negative pressure, and though the percentage of CO_2 recorded was 90 per cent by volume the tension of CO_2 was much less than the percentage would indicate. In the experiments recorded in this study, however, the concentrations given represent the corresponding tensions of CO_2, since the system was open. Since, however, even a concentration of 54.5 per cent of carbon dioxide is beyond the limits found in the body under normal conditions, the effect of CO_2, in so far as it may directly influence the growth of tubercle bacilli in the body, can be definitely excluded as a factor in organic tuberculosis; and the more extensive pulmonary disease which is seen in animals cannot be attributed to a lower CO_2 tension present in the alveolar air as compared to the slightly higher tension of carbon dioxide in the sinusoids of the liver.

THE GROWTH OF TUBERCLE BACILLI IN AN ATMOSPHERE OF ALVEOLAR AIR COMPARED WITH THOSE GROWING IN THE GASEOUS ATMOSPHERE OF MIXED VENOUS BLOOD

In a series of preliminary experiments it was found, in agreement with Novy, that within certain limits the rate and luxuriance of the growth of tubercle bacilli are directly proportional to the O_2 tension of the gaseous environment. Tubercle bacilli grow less rapidly in an atmosphere of lower oxygen tension than in one of higher oxygen tension.

In view of the opposite positions of the lung and liver in their susceptibility to tuberculosis, it seemed advisable to determine by experiments *in vitro* whether tubercle bacilli are sufficiently sensitive to differences in their gaseous environment to be affected by differences in the gas tensions which are present in the animal body. Therefore, the gas tensions

of the alveolar air and those of mixed venous blood were chosen, as suitable for study, in order to determine whether tubercle bacilli grow more rapidly in an atmosphere resembling, in composition, alveolar air than in an atmosphere resembling the gases of mixed venous blood, and in order also to elucidate pulmonary *susceptibility* as contrasted to hepatic *resistance* to tuberculosis.

According to the work of L. J. Henderson and others (5), the alveolar air has an oxygen tension of 100 mm. and a carbon-dioxide tension of 40 mm., while the mixed venous blood has an oxygen tension of 35 mm. and a carbon-dioxide tension of 47 mm. In order to convert these gas tensions into percentage concentrations, the atmospheric conditions as they are found in Denver were taken into consideration.

The average atmospheric pressure of Denver for ten years, as given by the *Report* of U. S. Weather Bureau, is 628 mm. Therefore, the oxygen tension in the alveolar air is equal to $\frac{100}{628} \times 100$, or 15.94 per cent oxygen, and the carbon dioxide, $\frac{40}{628} \times 100$ or 6.37 per cent carbon dioxide. In this way the figures for venous blood are

$$\frac{47}{628} \times 100 = 7.48 \text{ per cent } CO_2$$

$$\frac{35}{628} \times 100 = 5.57 \text{ per cent } O_2$$

The experiment was divided into three series as follows:

Series A: A comparison of the growth of tubercle bacilli in an atmosphere of alveolar air, that is, 15.94 per cent O_2 and 6.37 per cent CO_2, with the growth in atmospheric air.

Series B: A comparison of the growth of tubercle bacilli in the gaseous atmosphere of mixed venous blood, that is, 5.57 per cent O_2 and 7.48 per cent CO_2, with the growth in atmospheric air.

Series C: The same suspension of tubercle bacilli was then used to seed three sets of culture tubes, one maintained during growth in an atmosphere of alveolar air, a second set in an atmosphere of the gases of mixed venous blood, and a third set in atmospheric air.

The general plan of the experiment was identical to that described for carbon dioxide, the continuous-flow open system being used.

In the preparation of the gas mixtures the following equations and calculations were made use of:

The cylinder gases used in this study upon analysis revealed:

1: The carbon dioxide consisted of CO_2 = 96.0 per cent; O_2 = 0.44 per cent; other gases (mostly nitrogen), 3.56 per cent.

2: The nitrogen was practically 100 per cent pure.

Upon analysis the air used was composed of 20.98 per cent O_2 and 0.03 per cent CO_2, the remainder being nitrogen.

If a gas-mixture of alveolar-air composition, with CO_2 6.37 per cent, O_2 15.94 per cent, and inert gases 77.69 per cent, was desired, a 90-litre tank of this gas, was determined as follows:

90×0.0637, or 5.733 litres of pure CO_2.
90×0.1594, or 14.346 litres of pure O_2.
90×0.7769, or 79.921 litres of other gases.

x = number of litres of 96 per cent CO_2 to be taken,
y = number of litres of ordinary air to be taken.

$$\frac{5.733 - 0.0003y}{0.96} = x$$

$$\frac{14.346 - 0.0044x}{0.2098} = y$$

In solving,

x = 5.950 litres carbon dioxide,
y = 70.0 litres air,
$90.0 - (5.95 + 70.0) = 14.05$ litres nitrogen.

The detailed data of series A and B are omitted here, since essentially the same results were obtained in series C, which includes the combined points. In series A it was found that tubercle bacilli grow slightly better in an atmosphere of alveolar air than they do in ordinary atmospheric air, in spite of the fact that the oxygen tension of the alveolar air is considerably less than that of atmospheric air. In the studies with different concentrations of carbon dioxide and constant atmospheric oxygen tension, it was found that tubercle bacilli grow slightly better when 14.5 per cent carbon dioxide is present than in ordinary atmospheric air. It would seem, therefore, that the slight inhibition of the growth of tubercle bacilli, consequent upon the reduction of the oxygen tension, from the 21 per cent of an atmosphere in Denver, that is, 131.7 mm., to the oxygen tension of alveolar air, that is, 100 mm., is overcompensated by the stimulating effect of the 40 mm. of carbon-dioxide tension present in the alveolar air as compared to 0.19 mm. of carbon-dioxide tension present in the atmospheric air.

The tubercle bacilli maintained (series B) in an atmosphere of venous blood, that is, in an oxygen tension of 35 mm. Hg and a carbon-dioxide tension of 47 mm., did not grow as well as tubercle bacilli maintained in

TABLE 3

The growth of tubercle bacilli in vitro in gas mixtures of alveolar-air composition (6.37 per cent carbon dioxide, 15.94 per cent oxygen), of the gases of mixed venous blood composition (7.48 per cent carbon dioxide, 5.57 per cent oxygen) and for control in atmospheric air

	TUBERCLE BACILLI	ONE WEEK			TWO WEEKS			THREE WEEKS			FOUR WEEKS		
		Alveolar	Venous	Control	Alveolar	Venous	Control	Alveolar	Venous	Control	Alveolar	Venous	Control
Growth recorded on eleven different culture tubes	Gluckson	0*	0	0	41,12	0	11	51,62	91	41,22	32,33,24	82,23T	21,42,33
	Human avirulent	11	0	0	102,13	31,62,13	71,22	32,23,34	32,63T	21,62,23	23,34	32,23,34T	12,73
	Bovine virulent	31	0	31	102	21,92	21,82	12,93	62,53T	52,53	12,33,44	32,43,14T	63,14
	Bovine D	0	0	0	101,12	41	71	82	61,42T	31,72	22,13	11,82T	11,72

* The growth of the tubercle bacilli on the media is graded as in table 1 from 0 = no visible growth to 4 = a pronounced and luxuriant growth covering the entire medium.

The special markings in this table include T = thin. This designation means that the growth is thin and veil-like, rather than the usual normal thick corrugated growth obtained for tubercle bacilli under normal atmospheric conditions on suitable media.

atmospheric air. In this case the inhibition of growth due to the reduction of the oxygen tension from 131.7 mm. Hg. to 35 mm. is not compensated by the stimulating effect of the 47 mm. of carbon-dioxide tension, and the growth in the atmospheric air is distinctly better.

The experiment (series C) recorded in table 3 corroborated the findings of series A and B; but it is more conclusive, since the same suspension of tubercle bacilli was used for seeding the three sets of culture-tubes, and the tubes were kept under identical conditions of temperature, moisture, etc., except that the composition of the gases flowing over them differed. The findings in series C leave no doubt (1) that tubercle bacilli grow better in an atmosphere of alveolar air than in atmospheric air, (2) that those grown in an atmosphere of venous blood show less growth than those in atmospheric air and (3) that those grown in an atmosphere of alveolar air thrive far better than those grown in an atmosphere of venous blood. The tubercle bacilli grown in an atmosphere of the gaseous composition of the mixed venous blood assume a very thin veil-like appearance, and appear in marked contrast to the usual corrugated, thick, heavy growth usually seen in cultures grown in atmospheric air. This difference is well depicted in the appended illustrations. The same veil-like growth occurs, as will be shown later, when tubercle bacilli are grown in low tensions of oxygen.

The gaseous environment of tubercle bacilli in the lung: With regard to the gaseous environment of tubercle bacilli growing in the lung on the one hand, the liver on the other, and in the remaining organs considered in this study, the cell of origin of the tubercle may be of significance, yet opinion at present is divided regarding these cells. Whether the endothelial cells of the pulmonary capillaries are the cells of origin of the tubercle in the lung, as maintained by Foot, or whether the parent cells are the histiocytic elements of the lung-tissue, as maintained by Lang (Maximow), or the alveolar epithelium as claimed by Aschoff and Sewall, or, finally, the monocyte, for which recently Sabin and Cunningham have produced evidence (6), it seems that, so far as the gaseous environment of the bacilli is concerned, no essential difference has been shown to exist. Whatever the cell of origin of pulmonary tubercle may be, it is located in the alveolar walls or in their immediate proximity. Furthermore, in the exudative and pneumonic types of pulmonary tuberculosis, which play no small rôle in this disease in the lung, the epithelioid cells bearing the multiplying bacilli, whatever be their origin, are commonly located in the alveolar spaces themselves, and the cells at the periphery of such

tuberculous processes are directly exposed to the atmosphere of the alveoli. The atmosphere in the alveoli comprises the highest oxygen tension of any found in the body. Therefore, the rate of growth of the bacilli in these tubercles should be more rapid than in an organ like the liver, with a circulation composed of a mixture of venous and arterial blood. It may be intimated that while tubercle bacilli growing in the lung are exposed, on the one hand, to the aveolar air, they are exposed, on the other hand, to the gases of the venous blood, as it flows through the pulmonary capillaries, but the direction of the flow of oxygen is not from the blood to the alveolar air but just the opposite. The source of oxygen of both the blood in the capillaries and of the cells of origin of the tubercle is the alveolar air; and its oxygen tension, due to the delicate regulation of the mechanism of respiration, is always approximately the same, and is not appreciably diminished. Thus, it seems safe to assume that tubercle bacilli growing in the lung in all the species studied grow in an atmosphere approximating 100 mm. of oxygen and 40 mm. of carbon-dioxide tension, a higher oxygen tension than is found elsewhere in the body.

The gaseous environment of tubercle bacilli in the liver: The blood of the liver sinusoids is poor in oxygen as compared with the tension in the lung and, although it is at present impossible to directly determine the oxygen tension of the capillary blood, an examination of the available data permits an approximate estimation of the tension in the liver sinusoids as well as in other capillary beds of the body. The blood circulating in the liver sinusoids differs from that in the spleen, kidney and bone-

The effect of different oxygen tensions on the growth of tubercle bacilli

FIGURE 1

A: The growth of virulent human tubercle bacilli on glycerol-agar.

6: Atmospheric air equals 132 mm. oxygen tension in Denver. *8:* 3.8 mm. oxygen tension in Denver (about 0.5 per cent at sea-level). *10:* 0.8 mm. tension in Denver (about 0.1 per cent at sea-level).

FIGURE 2

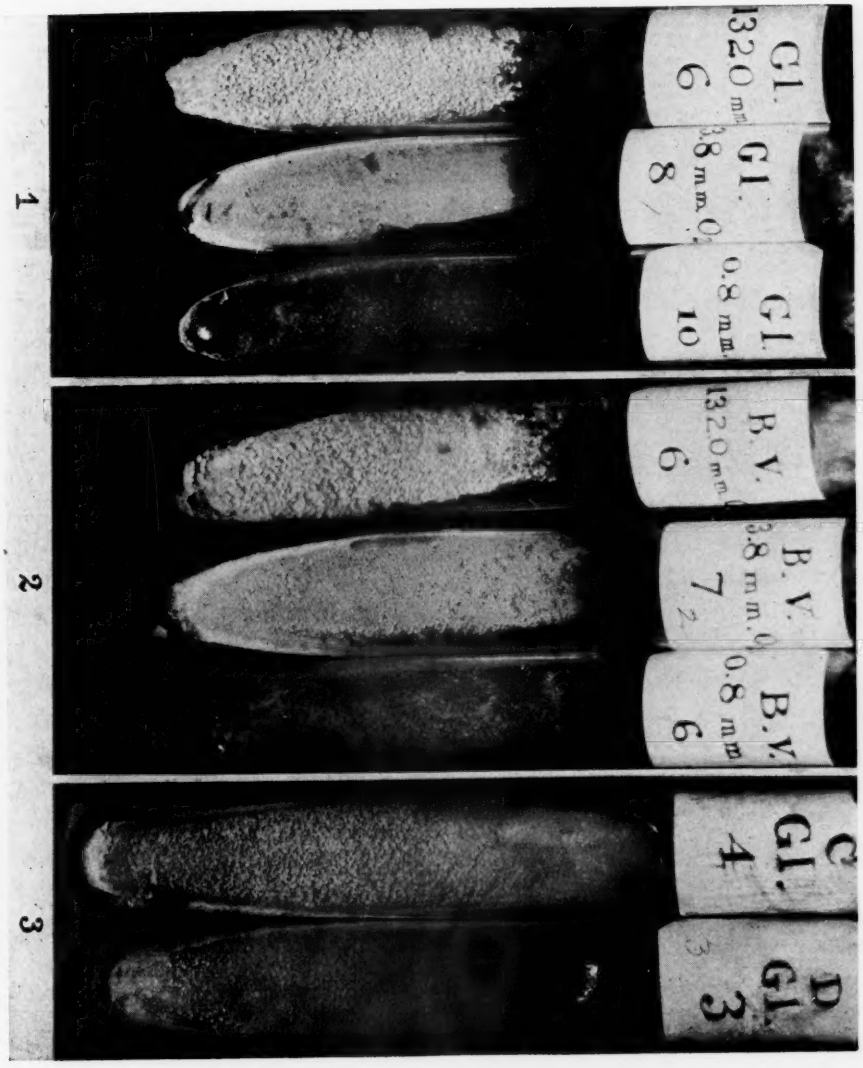
B: The growth of virulent bovine tubercle bacilli on glycerol-agar.

6: (left tube) Atmospheric air equals 132 mm. oxygen tension in Denver. *7:* 3.8 mm. oxygen tension in Denver (about 0.5 per cent at sea-level). *6:* (right tube) 0.8 mm. tension in Denver (about 0.1 per cent at sea-level).

FIGURE 3

Comparison of the growth of tubercle bacilli in atmospheres of alveolar air and mixed venous blood composition. Growth of virulent human tubercle bacilli on glycerol-agar.

C: Gases of alveolar air, 100 mm. O_2 + 40 mm. CO_2. *D:* Gases of mixed venous blood, O_2 = 35 mm., CO_2 = 47 mm.


Gl.
1320 mm.
6
Gl.
3.8 mm.
8
Gl.
0.8 mm.
10
B.V.
1320 mm.
6
B.V.
3.8 mm.
7
B.V.
0.8 mm.
6
C
Gl.
4
D
Gl.
3
1
2
3

marrow in that, in the latter, arterial blood enters the capillaries, while both venous and arterial blood enter the liver sinusoids.

The studies of Burton-Opitz (7) on the relative quantities of arterial and venous blood coming to the liver are of value in this connection. For each 100 gm. of liver-tissue the dog receives 25 cc. of arterial blood and 59 cc. of venous blood per minute. If these figures are representative of the species included in this study, and if it is assumed that the arterial blood enters the liver at its highest state of saturation, that is, with an oxygen tension of 100 mm., and that the blood of the portal vein has an oxygen tension of mixed venous blood, that is, 35 mm. Hg, then the mixture consists of 25 volumes at 100 mm. and 59 volumes at 35 mm. Hg, or an average of $\frac{25 \times 100 \text{ mm.} + 59 \times 35 \text{ mm.}}{84} = 54 \text{ mm.}$ of oxygen tension in the blood entering the liver sinusoids. As the blood flows along the liver sinusoids its oxygen load is gradually diminished until it reaches the hepatic venules, where the oxygen tension may be assumed to be that of mixed venous blood. Therefore, the blood enters the liver sinusoids at 54 mm. and leaves it at 35 mm., the mean between these extremes being about 45 mm. of oxygen tension existing in the blood of the liver sinuoids.

Tubercles in the liver originate from the Kupffer cells. The oxygen supply for these cells is the blood circulating in the liver sinusoids. Therefore, it would seem that the cells, in which the tubercle bacilli live, have an oxygen supply, the mean tension of which is 45 mm. Hg.

The blood entering the capillaries of the spleen, kidney, and bone-marrow is unmixed arterial blood. If the arterial blood has the same oxygen tension as the alveolar air, namely 100 mm. Hg, and the blood of the capillaries of these organs leaves the capillaries at an oxygen tension of mixed venous blood or 35 mm. of oxygen tension, then the mean oxygen tension of the blood of the capillaries of these organs is 67 mm. Hg. The oxygen tension of the source of oxygen for the cells in which the tubercle bacilli grow is therefore, in the case of the lung, 100 mm., in the case of the liver 45 mm. and in the case of the spleen, kidney and bone-marrow 67 mm. Hg.

In the above *in vitro* experiments tubercle bacilli grew better in an atmosphere of alveolar air than in one of the gases of mixed venous blood, and it seems fair to assume therefore that tubercle bacilli will grow more rapidly in the lung than in the spleen, kidney and bone-marrow, and in all the foregoing organs more rapidly than in the liver.

It would appear, then, that one reason for the predominance of pulmonary tuberculosis over involvement of the other organs of the body in all the species studied is presumably a more rapid growth or multiplication of the bacilli in this organ, due to the fact that the source of oxygen, the alveolar air, for the cells of the tubercles in the lung has the highest oxygen tension of any other cellular source of oxygen in the body.

The liver, occupying an opposite position to the lung, frequently escapes the disease, and the tubercles tend to be the smallest in the body, because the mean oxygen tension of the blood of the liver sinusoids is lower than that of any other organ in the body.

In the spleen, kidney and bone-marrow the tubercle bacilli can grow less rapidly than in the lung and more rapidly than in the liver, in great part because the mean oxygen tension of the capillary blood of these organs is lower than that of the alveolar air, on the one hand, and higher than the mean oxygen tension of the blood of the liver sinusoids, on the other.

The information gained from the study of the distribution of the tubercle bacilli to the organs of the different species of animals after intravenous inoculation, together with the above findings on gaseous environment, make more intelligible the variability of organic involvement developing in the different species. Thus, the predominance of the disease in the rabbit's lungs, in spite of the low original seeding with living tubercle bacilli, can be attributed to a more rapid growth of the bacilli in this organ, which is due to a more favorable gaseous medium. The escape of the liver from massive tuberculous disease, in spite of heavy seeding with bacilli, can be attributed, in part at least, to the slow growth of the bacilli in this organ as compared with any other organ in the body. The tubercles in the spleen, kidney, and bone-marrow in the rabbit are approximately of the same size, and the number of tubercles correspond with the seeding, which would favor the view that the tubercle bacilli grow equally rapidly in all these three organs, due to the equal oxygen tension of the capillary blood.

In the guinea pig the excess of tuberculous disease in the lung over that in the liver for the first four weeks after infection, in spite of the much greater seeding of tubercle bacilli in the liver, may again be correlated with the higher oxygen tension of the alveolar air, as compared with the lower oxygen tension of the blood of the liver sinusoids. That

the amount of disease in the liver finally overtakes that in the lung may be accounted for by the heavier seeding in the liver, which outweighs the low oxygen tension and consequently slower growth of bacilli in this organ, with the result that there occur more numerous though smaller coalescing foci and greater involvement. More tuberculosis develops in the spleen than the liver for two reasons: the oxygen tension in the capillaries of this organ is higher than that in the liver sinusoids and, in addition, the deposition of tubercle bacilli in the spleen is greater than in the liver. The rarity of involvement of the kidney in the guinea pig is accounted for by the small deposition of tubercle bacilli in this organ.

The peculiar alternate and opposite tuberculous involvement of the lung and liver in the guinea pig after intravenous infection would seem to find at least a partial explanation in the light of the above observations. A massive disease in the lung and a relatively slight affection of the liver is found during the first four weeks after intravenous infection, and particularly when large doses (0.1 mgm.) of bacilli are introduced into the circulation. Now, when large doses of bacilli are introduced, although the lung arrests a relatively smaller amount of bacilli than does the liver, still a considerable number are deposited in the lung. Since the growth of the bacilli in the lung is more rapid than in the liver, the original foci in the lung, though much less numerous than those in the liver, will attain a considerable size while the foci in the liver will still be minute because of the less rapid multiplication of the bacilli in this organ. Then the rapidly growing foci in the lung will further materially interfere with the oxygenation of the blood, and thus will result a further diminution of the oxygen of the blood of the liver sinusoids, with the result that the growth of the bacilli in the liver under these conditions will be more depressed than in a normal animal and, as a consequence, the tuberculosis is held in abeyance. When small doses are injected, only a few tuberculous foci localize in the lung, and, though the tubercles develop faster in the lung than they do in the liver, the foci present will be so few that they cannot materially influence the oxygenating function of the blood and the growth of the original foci in the liver is not as markedly depressed, so that even though these early foci are smaller than the early foci in the lung there are many more of them present and their coalescence results in a much more extensive disease in the liver than occurs in the lung in this case.

In the liver the tubercles develop after intravenous infection mainly at the periphery of the lobule. One explanation for this is the greater

deposition of the bacilli at this place. A contributory but probably less important explanation for this may be that the oxygen tension of the blood of the liver sinusoids is greater at the periphery than toward the centre of the lobule; hence the possibility of a slightly more rapid growth of the bacilli situated on the periphery.

In Study I of this series (8) the difference in the distribution of the disease in the guinea pig after the intravenous and the subcutaneous modes of infection was pointed out. The first four weeks after intravenous infection, tuberculosis is more extensive in the lung than in the liver, while after subcutaneous infection the pulmonary disease is at all times less extensive than the hepatic disease. This difference may, to a certain extent, be accounted for by the fact that with the intravenous modes of infection the major seeding of the organs is accomplished at once, while with the subcutaneous mode of inoculation, the original subcutaneous focus floods the lymph channels with bacilli more or less continuously or intermittently over a long time, and thus the organs are continuously being seeded with bacilli. Since the number of bacilli escaping from the original focus at any one time must be few and since the "open lung" factor of the guinea pig (Krause) is operative, the number of bacilli deposited in the lung early in the infection must indeed be very small, while the liver contains a far greater number of bacilli. It would seem, therefore, that perhaps the difference in the organic distribution of tuberculosis after the intravenous or subcutaneous modes of infection may be accounted for to some extent at least in the light of the knowledge on the rate of growth of the bacilli in these two organs, as controlled by the oxygen supply available for them. In the case of intravenous infection, especially when the dose is large, the seeding in the lung is considerable, so that the more rapid growth of the bacilli in the lung asserts itself, and the resulting tuberculosis in the lung is extensive, while the tuberculosis in the liver is sufficiently retarded, so that, though the original foci are more numerous in the liver, they are very minute. In the case of subcutaneous infection, even with large doses, the amount of bacilli that escape into the circulation at any time is minute and the seeding of the lung is negligible, while in the liver the additions are greater, and the protective factor of the low oxygen tension of the blood is finally overcome, so that the tuberculosis in the liver at last becomes apparent while the lung is still uninvolved or only slightly involved.

In the monkey the organic tuberculosis following intravenous infection

with living bacilli may, to a great extent, be accounted for by the distribution of the bacilli to the different organs, and the rate of growth of these bacilli in the organs as controlled by the oxygen tension about the epithelioid cells in which the bacilli grow. The invariably larger size of the pulmonary tubercles is accounted for by the more rapid growth of the bacilli in the lung. The occasional absence of hepatic disease and the small size of the individual hepatic tubercles are accounted for by the low oxygen tension of the sinusoidal blood. The massiveness of the disease in the spleen can be attributed to the large seeding of tubercle bacilli in this organ. The excess of the hepatic disease, in the majority of cases, over that in the lungs may be accounted for by the overcoming of the inhibition of the growth of the bacilli as a result of greater seeding in the liver, so that more tuberculosis results from the coalescence of smaller but more numerous foci. The approximately equal size of the individual tubercles in the spleen, kidney and bone-marrow is attributable to the same oxygen tension available for the epithelioid cells containing the tubercle bacilli in these three organs. The massiveness of the disease in the bone-marrow of the monkey cannot be explained on the basis of the seeding, since the deposition of carbon in this organ is only slightly greater than that in the lung. Other factors will have to be sought in explanation of this. In all the four species of animals studied, oxygen tension played a rôle in the development of organic tuberculosis, but there still remain some peculiar discrepancies in the different species, in so far as the quantitative relations of tuberculosis are concerned. Compare, for example, the involvement of the spleen and liver of the four species. In all four species the oxygen tension in the liver sinusoids or the oxygen tension of the splenic capillaries is presumably approximately the same, the tension in the former being lower than the latter. The relative seeding of tubercle bacilli to these two organs is the same, there being more per gram of tissue in the spleen than in the liver, yet entirely different amounts of tuberculous involvement occur in the same organ in the different species studied. In the case of the rabbit there is very little macroscopic tuberculosis in the liver, while in the dog the involvement following moderate infecting doses is massive. In the guinea pig the spleen is the site of massive tuberculous involvement, while the dog's spleen usually fails to develop any disease. In the guinea pig the liver early becomes only slightly involved, while later the involvement is extensive, while the rabbit's liver never becomes extensively involved. In the monkey the spleen is extensively involved, while in the rabbit

there only occurs a moderate involvement. These facts alone make it evident that there are additional factors concerned in organic susceptibility to tuberculosis, which have nothing to do with the distribution or deposition of the bacilli following intravenous injection or with the oxygen tension of the source of oxygen for these tissues and the bacilli.

It was, however, the striking tuberculous involvement in the dog which suggested further study. In the dog, too, the oxygen tension plays a rôle, since, with small doses of tubercle bacilli, the lung is the only organ that becomes involved, because the oxygen tension of the alveolar air being higher than that in any other part of the body permits the tubercle bacilli to grow more rapidly. The larger size of the individual tubercles in the lung of the dog, as compared with that of any other organ with larger infecting doses of bacilli, is due to the same factor. In explanation of the extensive disease in the liver of the dog, a heavier seeding than in the lung may be suggested, but, relatively, the deposition of the bacilli in the dog's liver is not greater than in the rabbit's liver, and yet the rabbit does not develop hepatic tuberculosis. It was thought that perhaps the more rapid dissociation curve of the oxyhemoglobin of the dog's blood as compared with that of the rabbit's blood, as pointed out by Barcroft and Camis (9) (10), might be of some significance in explaining this difference in the hepatic susceptibility to tuberculosis in these two species. If the blood entering the liver sinusoids of the rabbit has the same oxygen tension as that of the dog, there is a greater dissociation of the blood of the dog, and more oxygen will be given up to the tissues, which results in more oxygen being available for the growth of the tubercle bacilli in the dog's liver than in the case of the rabbit. This difference, as Barcroft and Camis point out, is accounted for in that the dog's corpuscles contain chiefly sodium salts while rabbit and human corpuscles contain chiefly potassium salts. The dissociation curve of the dog's blood may account, to some extent, for the greater amount of tuberculosis in the dog's liver than in that of the rabbit, but the organic seeding and oxygen factor cannot explain the absence of splenic tuberculosis in the dog, for in the spleen bacilli are localized to a greater degree than in the liver, and the oxygen tension of the splenic capillary blood is higher than that of the liver sinusoids. If the peculiar dissociation curve of the dog's blood plays a rôle in increasing the amount of tuberculosis in the liver it should act in the same way in the spleen. Therefore, other factors must be sought to explain some of the peculiar discrepancies noted above.

THE EFFECT OF LOW OXYGEN TENSIONS ON THE GROWTH OF TUBERCLE BACILLI

In the early part of this paper emphasis was laid on the gaseous atmosphere surrounding the cells in which the tubercle bacilli live, that is, the alveolar air and the gases of the capillary blood, but no mention was made of the oxygen tension of the cells themselves, since this is at present

TABLE 4

The growth of tubercle bacilli in vitro in an atmosphere of 0.12 per cent oxygen (0.10 per cent at sea-level)

	TUBERCLE BACILLI		TWO WEEKS		FOUR WEEKS		SIX WEEKS	
			Exposed	Control	Exposed	Control	Exposed†	Control
Growth recorded on 5 different tubes	Gluckson	Gentian-Violet-egg medium	0*	21,22	0	23,34	0	13,44
		Glycerol-Agar	0	31	0	33,24	0	23,34
	Human avirulent	Gentian-Violet-Egg Medium	0	21,32	0	54	0	54
		Glycerol-Agar	0	41,12	0	33,24	0	13,44
	Bovine Virulent	Gentian-Violet-Egg Medium	0	32,23	0	54	0	54
		Glycerol-Agar	0	31,22	0	13,44	0	13,44
	Bovine D	Gentian-Violet-Egg Medium	0	52	0	54	0	54
		Glycerol-Agar	0	31,22	0	54	0	54

* The growth of the tubercle bacilli on the media is graded as in table 1 from 0 = no appreciable growth to 4 = a luxuriant growth, the left integer indicating the number of tubes and the right the grade of growth obtained. See table 1 for explanation.

† After six weeks' incubation with 0.12 per cent oxygen all the tubes were restored to atmospheric air and incubated, when the majority of the *Bovine Virulent*, *Human* and *Bovine D* tubes gave luxuriant growth at incubator temperature but none of the *Gluckson* tubes grew.

not known with any degree of accuracy. Within recent years Argyle Campbell (11) has attempted to approach the solution by injecting different gases under the skin or into the peritoneal cavity of animals, and determining the carbon dioxide and oxygen tensions at different intervals of time and under different conditions. It was found, among other things, that in a general way the conditions which favor the dissociation of oxyhemoglobin increase the oxygen tension of the tissue-

spaces. It is admitted that this is still a far cry from the determination of the actual gas tensions in the cells, but it is a nearer approach than the results obtained in determining the gas tension of the blood. Campbell found that thirty-six hours after the injection of atmospheric air into the subcutaneous tissues of rabbits the oxygen tension is 20–30 mm. Hg. Now, whatever be the actual oxygen tension in the tissue-cells, it must be low; therefore, the growth of tubercle bacilli in atmospheres of low oxygen tension becomes important. Novy and his coworkers found that tubercle bacilli could live in an atmosphere containing even 0.5 per cent oxygen. It seemed desirable to determine by the open method the lowest oxygen tension under which tubercle bacilli would grow.

In series A a gas containing 0.12 per cent oxygen (equivalent to 0.10 per cent oxygen at sea-level in its oxygen tension) and in series B a gas containing 0.61 per cent oxygen (equivalent to 0.50 per cent oxygen at sea-level) were used. The remainder of the gas consisted of nitrogen. Nitrogen manufactured by the Linde Air Products Co., Cleveland, Ohio, was used without modification in series A. On analysis, this gas contained 0.10 per cent oxygen. In making the gas mixture for series B a calculated amount of air was introduced into the reservoir tank, and the deficit made up from the nitrogen gas up to a definite volume.

The ordinary Hempel's Apparatus and Method (*Gasanalytische Methoden (1900) p. 48 ff*) did not prove accurate enough for the analysis of the small amounts of oxygen and carbon dioxide present in the gases during this experiment, so that an apparatus was constructed on the principles embodied in the Haldane-Henderson Gas Analyzer. In the modified apparatus the 4-way stopcock was discarded, and two additional 3-way stopcocks were installed, so as to facilitate the taking in of gas samples and the expulsion of the residual gas. The burette was entirely enclosed in a water jacket. The total capacity of the burette was 21 cc., while the stem had a capacity of 6 cc. and was graduated to 0.01 cc. The remaining parts of the apparatus were essentially identical to the Haldane-Henderson Respiratory Analyzer (12).

The method and general plan of the experiment for exposing the tubercle bacilli to the gas, etc., were identical to the previous experiments recorded in this study. The detailed growth charts for the tubercle bacilli grown in an atmosphere of 0.5 per cent O_2 are omitted for obvious reasons. It was found, in general, that the growth of tubercle bacilli in 0.5 per cent oxygen is markedly inhibited, as compared with tubercle bacilli grown in atmospheric air. Only a slight growth is

apparent after six weeks' incubation, while controls grown in atmospheric air and seeded from the identical suspension show a luxuriant and profuse growth after this time.

Tubercle bacilli supplied an atmosphere containing only 0.1 per cent oxygen completely fail to grow, even after six weeks' incubation at 37°C.

Though there was no evidence of growth after six weeks at 37°C. with an oxygen tension of 0.10 per cent, a change to atmospheric air for 5 weeks resulted in growth, as is recorded in a footnote to table 4, in all the strains studied except the virulent human strain of bacilli, *Gluckson*, which peculiarity was not accounted for in this study.

SUMMARY

1. These studies emphasize the importance of slight changes in oxygen tension upon the growth of tubercle bacilli, and appear significant in the flaring up of old tuberculous lesions in man with resultant progressive and fatal disease, since conditions which can change the oxygen tension in tuberculous foci from 0.7 mm. to 3.8 mm. of oxygen tension may be sufficient to change a completely quiescent focus into progressive disease.

2. The studies also make it apparent that changes in bodily conditions which can alter the oxygen dissociation curve of the blood may exert a marked influence upon the progress of the disease. If the flow of oxygen to the tissues is increased, dormant tubercle bacilli in these tissues may multiply.

3. One of the most important single factors influencing the oxygen dissociation curve of human blood is its state of hydrogen-ion dissociation. Those conditions, such as fatigue and starvation, which tend to increase the hydrogen-ion concentration of the blood, and which therefore increase the rate of dissociation of oxyhemoglobin, also influence in a deleterious way for man the progress of the disease, while factors, such as rest and adequate nourishment which tend to decrease the hydrogen-ion concentration of the blood and thus depress the dissociation of oxyhemoglobin, have a beneficial effect on tuberculosis; for thus the oxygen available for the tissues is reduced and the growth of the bacilli in the tuberculous lesions is retarded.

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ASPIRATION TUBERCULOSIS IN RABBITS

AN X-RAY STUDY OF THE DEVELOPMENT OF THE TUBERCULOSIS OF PRIMARY INFECTION AND THAT OF SUPERINFECTION[1]

WILLARD B. SOPER, HOMER L. SAMPSON AND CHARLES H. HASKINS

In 1920 Mullin and Ryder (1) reported on the production of experimental lesions of the lungs by the instillation of fluid into the nose of rabbits: "in five of six animals the maximum effect was produced in one upper lobe." In 1922 Corper and Robin (2), and later Corper (3) alone, experimented extensively with this method of infection, and observed that particulate matter, as well as killed tubercle bacilli, when aspirated in fluid suspension, had a tendency to localize and remain for a relatively long time in the finest pulmonary divisions. Their observations indicated strongly that the localization of fluids aspirated into the lungs is largely determined by physical forces, chiefly gravity and inspiratory suction.

A very simple method for producing tuberculosis of one lung in the experimental animal seemed at hand. In an effort to solve certain artificial-pneumothorax problems, it was decided to produce one-sided disease by the method of Mullin and Ryder, employing rabbits which were sensitized subcutaneously before pulmonary infection. Accordingly four rabbits were used to confirm the findings of Mullin and Ryder, and of Corper, as to the localization of the lesions. X-ray studies of these animals proved so interesting that it was decided to enlarge the investigation, first, from a radiographic standpoint, and, later, from the radiographic supplemented by the pathological approach. This paper gives the results of the earlier radiological study.

TECHNIQUE

Rabbits were used exclusively. The first set of 4 animals was used primarily to determine what superinfecting quantity of virulent bovine bacilli would best produce the lung lesion desired. After a preliminary sensitization with human tubercle bacilli subcutaneously in the groin,

[1] From the Saranac Laboratory for the Study of Tuberculosis, Saranac Lake, New York.

2 of the 4 rabbits were each given 1 mgm. of dried bovine bacilli (Saranac Laboratory strain B1) in 2 cc. of physiological salt solution by the Mullin and Ryder method of instillation into the nose. The other two rabbits each received 0.5 mgm. of the same strain of bovine bacilli into the nose. X-ray films, made nineteen days after this pulmonary infection, showed so little definite pulmonary lesion that a second superfection was tried, this time with larger doses. The two rabbits, which had received 1 mgm. of bovine bacilli into the lung, were now given an additional 5 mgm. in suspension, and the 2 which had received 0.5 mgm. of bovine bacilli received an additional 2.5 mgm. of B1.

The reactions in all 4 animals were now so striking that 8 other rabbits were added to the experiment: 4 of them normal unsensitized rabbits, to serve as controls, and 4 of them sensitized identically like the preliminary four. In all 8 the larger doses of bovine bacilli were used: a suspension of 5 mgm. of dried bovine bacilli in 2 cc. of physiological salt solution in half of the rabbits, and 2.5 mgm. of dried bacilli in 1 cc. suspension in the others. (We recommend that the bacilli be suspended ordinarily in only 1 cc. of fluid. The second cubic centimetre is aspirated less readily than the first.)

All animals were anaesthetized, preferably to the point of loss of the swallowing reflex. They were held, lying always on the right side, so that the infection would tend to locate in that hemithorax. The head was supported upright, and the fluid slowly injected into one nostril with a *Record* syringe. After infection the animals were left lying on the right side while the anaesthesia wore off.

Intracutaneous skin tests were performed in all rabbits before the intrapulmonary infection: 0.1 cc. of 10 per cent O. T. was used. As has often been remarked, the rabbit shows much less skin hypersensitiveness than the guinea pig, and this strength of tuberculin is necessary for reliable results.

X-ray films were made from time to time, more frequently in the beginning, and later at intervals of approximately one month. The animals for the most part were held lying prone upon the belly. Some films were made with the animal lying upon the back, since the heart shadow is not so large in this position. The report of X-ray examinations on each successive date, as given in the protocols, is a comparison of that film with the one taken immediately before.

PROTOCOLS

Rabbits 1, 3, 5, 7, 9, 11, 13 and 15 were all sensitized in identically the same manner. On August 4, 1925, they were injected subcutaneously in the right groin with 0.5 cc. of an emulsion of three-weeks-old human tubercle bacilli (strain H37), containing 1 mgm. of bacilli grown on glycerine-broth and dried between sterile blotting papers before weighing. These 8 rabbits constitute the group of superinfected animals as opposed to rabbits 10, 12, 14 and 16, the control animals, in which the intrapulmonary infection was primary.

Rabbit 1: Buck; 2721 gm., *August 4, 1925:* Sensitizing dose subcutaneously. *August 22:* Skin tested intracutaneously with 0.1 cc. of 10 per cent O. T. *August 24:* Reaction strongly positive (++++). *August 28:* Injected intranasally with 2 cc. of emulsion containing 1 mgm. of dried virulent bovine bacilli (strain B1). *September 16:* X-ray films showed only a questionable small amount of mottling at the right apex, and the left lung clear. Because more extensive reactions were desired, it was decided to repeat the intranasal injection with a larger dose. *September 17:* 2 cc. of an emulsion containing 5 mgm. of the same dried bovine bacilli were given. On September 24th, seven days after this second pulmonary infection, X-ray films were again made. Now there was marked homogeneous cloudiness in the upper two-thirds of the right lung. The dates and readings of subsequent X-ray examinations are:

September 16, 1925
R.: Questionably a small amount of mottling in the apex.
L.: No definite change.
September 24
R.: Marked homogeneous cloudiness in upper two-thirds (consolidation).
L.: Clear.
October 5
R.: Possible clearing of some of cloudiness in upper two-thirds.
L.: Clear.
October 15
R.: Clearing of some collateral haze in upper two-thirds.
L.: Clear.
October 26
R.: Questionable clearing of collateral haze in lower half.
L.: Clear.
November 16
R.: Definite clearing of some collateral haze in lower half.
L.: Clear.
December 14
R.: Possibly slight increase lower half.
L.: Clear.

January 18, 1926
R.: No definite changes in the shadows previously mentioned.
L.: Mottling in lower third.
February 12
R.: Increase of mottling in lower half.
L.: Increase of mottling throughout; ill-defined in upper third.
March 17
R.: Probable increase of mottling throughout.
L.: Definite increase of mottling throughout.

This animal was not apparently ill during the first three months, and there was a gradual increase of weight from 2777 gm. on September 12th to a maximum of 3316 gm. on November 18th. The weight maintained itself at this level through January 5, 1926. About this time dyspnoea was first noted, and from then on there was progressive loss of weight down to 1814 gm. on April 8th. The animal was found dead on April 14th, 229 days after the first pulmonary infection and 209 days after the second. It should be added that this animal developed tuberculosis of the nose, evidently from the nasal instillations. This was not manifest until the fourth month, when a moderate discharge was present, which contained acid-fast bacilli in fair number.

Autopsy: April 14, 1926: Both lungs uniformly riddled with large confluent tubercles about 3 mm. in diameter, of yellowish color, and cheesy and gelatinous in character. The pulmonary tissue between the tubercles much congested. Pleura nonadherent. No cavities found in the lungs. Liver and spleen apparently normal. Left kidney showed one tubercle, 1 mm. in diameter, on its surface. Right kidney normal. Peritoneum normal. Right nostril seat of tuberculous necrosis.

Rabbit 3: Buck; 2267 gm. Sensitized and infected intranasally at the same time and in a manner identical with rabbit 1. Intracutaneous skin reaction only weakly positive (+). On September 16, 1925, X-ray examinations, made nineteen days after the first pulmonary infection with 1 mgm. of bovine bacilli, showed only a questionable small amount of mottling in the root region on the right. Left lung clear. The second dose of 5 mgm. of bovine bacilli was given on September 17th, exactly as in rabbit 1. X-ray examinations of lungs resulted as follows:

September 24, 1925
R.: Development of marked cloudiness pretty much throughout upper three-fourths.
L.: Clear.
October 5
R.: Slight clearing of collateral haze in lower third.
L.: Clear.
October 15
R.: Clearing of collateral haze in lower half.
L.: Clear.

October 26

R.: Decided clearing of some of collateral haze in lower half.

L.: Clear.

November 16

R.: Clearing of some of collateral haze more or less throughou.

L.: Clear.

December 14

R.: No definite changes.

L.: Clear.

February 12, 1926

R.: Increase of mottling and cloudiness in upper two-thirds.

L.: Development of mottling and cloudiness in upper two-thirds.

March 17

R.: Mottling and localized cloudiness increased with more evidence of cavity formation in upper two-thirds. Probable pleurisy.

L.: Questionable cavity formation in upper third. (Cavity not found at autopsy.)

Heart shadow cannot be made out in last two examinations probably owing to increase in intensity of pulmonary process.

This rabbit, like no. 1, showed no early evidence of illness. It gained in weight, with slight remissions, up to 3202 gm. on January 5th. From then on there were progressive loss of weight and increasing dyspnoea. Also tuberculous snuffles became manifest during the fourth month. On April 13th this animal was found dead, 228 days after the first pulmonary infection and 209 days after the second infection.

Autopsy: April 13, 1926: The lower two-thirds of the right lung was a mass of homogeneous cheesy material of the consistence of semi-soft butter. The whole lung was bound to the chest-wall by adhesions, which could be broken only with difficulty. The diaphragm could be separated from the caudal lobe only by tearing into the cheesy mass. The upper third of the right lung was somewhat atelectatic and congested. The left lung showed a number of confluent tubercles, but only a moderately extensive involvement. No cavities were found in either lung. The liver, spleen and kidneys were macroscopically normal.

Rabbit 5: Buck; 2352 gm. Sensitized in a manner identical with rabbit 1. Intracutaneous test on August 22, 1925, gave good positive result (+++). On August 28th the animal was given intranasally half the dosage of bovine bacilli, which was given to nos. 1 and 3, that is, 1 cc. of emulsion containing 0.5 mgm. of B1. On September 16th X-ray examination, nineteen days after intrapulmonary infection with 0.5 mgm. of bovine bacilli, showed only a slight, questionable shadowing in the right upper lobe and nothing abnormal in the left lung. Therefore, an additional dose of 2.5 mgm. of bovine bacilli was given intranasally on September 17th, one-half the second dose given to rabbits 1 and 3. X-ray examinations of lungs showed:

September 24, 1925
R.: Development of marked cloudiness pretty much throughout.
L.: Clear.
October 5
R.: Increase of cloudiness toward the base.
L.: Clear.
October 15
R.: Clearing of some of collateral haze in lower half.
L.: Clear.
October 26
R.: Further clearing of cloudiness at base.
L.: Clear.
November 16
R.: Possibly further clearing of cloudiness at base.
L.: Clear.
December 14
R.: Definite clearing of cloudiness in lower half.
L.: Clear.

After taking the films on December 14th this rabbit was used for another experiment. At that time it weighed 2324 gm. as against 2352 gm. when the experiment began. Bovine bacilli and tuberculin were injected into the right pleural cavity at different times with a view of inducing exudate. Further films were made April 22, 1926, which showed extensive involvement of both lungs. Death occurred on June 3, 1926.

Autopsy: Both lungs, the right more than the left, showed extensive confluent areas of caseous pneumonia; there were marked adhesions on right, but no cavity formation.

Rabbit 7: Buck; 2380 gm. Sensitized and injected intranasally in a manner identical with rabbit 5. Intracutaneous test, August 24, 1925, medium strong positive (++). *September 16:* X-ray examination, nineteen days after intranasal injection of 0.5 mgm. of bovine bacilli, showed nothing abnormal in either lung. Accordingly, an additional intranasal dose of 2.5 mgm. of B1 was given on September 17th. On September 24th, seven days after the second intranasal dose, X-ray films showed marked cloudiness throughout the upper three-fourths of the right lung. The left lung was normal.

September 16, 1925
R.: No definite changes.
L.: Clear.
September 24
R.: Marked cloudiness throughout upper three-fourths.
L.: Clear.
October 5
R.: Increase of cloudiness extending toward the base.
L.: Clear.

October 15

R.: Probably a slight clearing in lower half.

L.: Clear.

October 26

R.: Definitely less cloudiness in lower half.

L.: Clear.

November 16

R.: Clearing of some of the cloudiness in lower half.

L.: Clear.

December 14

R.: Definitely a greater clearing of cloudiness in lower half.

L.: Clear.

January 18, 1926

R.: Film too delicate for interpretation. However, there is a suggestion of continued clearing in lower half.

L.: Questionable development of mottling in middle third.

February 5, 1926: Animal gradually increased in weight to 3032 gm. in November. Then weighed 3004 gm. Killed to establish character of snuffles mentioned under rabbits 1 and 3. The left nostril was found to contain necrotic material, which showed acid-fast bacilli in fair number. Also, the left eye showed a deep-seated corneal lesion. *Lungs:* Both caudal lobes were small and the seat of an early pneumonic process; the remainder of both lungs was seeded with hard shotty tubercles, translucent and with little or no collateral inflammation; no cavity formation. Liver, spleen and kidneys macroscopically normal.

Summary of Rabbits 1, 3, 5 and 7

The dosages of 1 and 0.5 mgm. of virulent bovine bacilli were apparently not sufficient to produce, within nineteen days, a marked pneumonic reaction in the lungs of rabbits previously sensitized subcutaneously with 1 mgm. of human tubercle bacilli. On the other hand, additional quantities of 5 and 2.5 mgm., arriving in the same lung, set up a pneumonia which caused a dense uniform shadowing over approximately the upper half of the lung in question. This pneumonic process underwent a decided clearing in all cases, to be followed subsequently by a further extension of disease and ultimate death of the animal. The nasal tuberculosis may well have had a bearing on the final general spread of the infection in these rabbits, through oft-repeated aspiration of bacillus-containing material. The rather unexpected general extension of the disease, subsequent to the earlier clearing of the X-ray shadow, was more or less coincident with the development of snuffles. The works quoted in the beginning of this article, as well as the experiences here recorded, suggest how relatively easily infection might have been borne from the nose to the lungs.

Rabbits 9, 11, 13 and 15 were also superinfected animals, but are distinguished from the above described four rabbits by the fact that they received only one dose of bovine bacilli into the lung.

Rabbit 9: Buck; 3004 gm. Received preliminary sensitization with human bacilli subcutaneously at the same time and in the same manner as rabbit 1. *August 24, 1925:* Intracutaneous test gave a moderately strong positive reaction (++); retested September 28th (++). September 30th, given intranasally 2 cc. of suspension containing 5 mgm. of a twelve-day-old culture of virulent bovine bacilli (strain B1), grown on glycerine-broth, and dried between sterile blotting papers before weighing.

October 5: X-ray examination, the fifth day after pulmonary infection, showed dense cloudiness pretty much throughout the upper three-fourths of the right lung. Left lung clear.

October 15, 1925
R.: Increase of mottling or cloudiness toward base.
L.: Clear.
October 26
R.: Questionable cavity. (No cavity at autopsy.)
L.: Development of mottling in lower half.
November 16
R.: Cavity formation in upper third questionable.
L.: No definite changes in shadows previously mentioned.
December 14
R.: No definite changes in shadows previously mentioned.
L.: Probable increase of mottling in lower half.
January 18, 1926
R.: Film very unsatisfactory for interpretation. However, there is no change in this side.
L.: Suggestion of increase throughout.
February 10
R.: Definite increase throughout.
L.: Definite increase throughout.

February 24, 1926: Animal found dead this morning. For the past several days it had been increasingly dyspnoeic, and had already begun to lose weight in January. Weight on November 2nd was 3287 gm.; on February 20th, 2352 gm.

Autopsy: Lungs showed a very extensive involvement of both lungs. They were the seat of mixed caseous, fibrous and pneumonic lesions with a preponderance of fibrosis which made the tissue difficult to cut. No cavity formation, and the small caseous areas appeared shot through with fibrous tissue. No adhesive pleurisy. Liver and spleen macroscopically normal. Both kidneys showed on the surface three old caseofibrous lesions ca. 1 mm. in diameter.

Rabbit 11: Buck; 3117 gm. Received preliminary sensitization at the same time and in the same manner as rabbit 1. *August 24, 1925:* Intracutaneous skin test gave strongly positive reaction (++++); retested September 26th (+++). On September 30th given intranasally 2 cc. of suspension containing 5 mgm. of virulent bovine bacilli.

October 5: X-ray examination on the fifth day after pulmonary infection showed mottling throughout the right lung, and a small amount of mottling in the lower half of the left lung.

October 15, 1925
R.: Increase of mottling in lower half.
L.: Probable slight increase of mottling in lower half.
October 26
R.: Cloudiness and mottling increasing throughout.
L.: Probable increase of mottling to lower half.
November 16
R.: Tendency to clearing in lower half.
L.: Tendency to clearing in lower half.
December 14
R.: Probable clearing in lower half.
L.: Probable clearing in lower half.
January 18, 1926
R.: Film somewhat unsatisfactory for interpretation. However, there is suggestion of more fibrosis with clearing in lower half.
L.: No definite changes in shadows previously mentioned.
February 10
R.: Definite clearing in lower half.
L.: Questionable faint traces of mottling.
March 17
R.: Possibly a little less collateral haze in lower half.
L.: No definite changes in shadows previously mentioned.
April 22
R.: Possibly a little more fibrosis in upper half.
L.: Development of infiltration (moderate) in upper half.

This animal showed a remarkable degree of clearing (see figures 4, 5 and 6), and on X-ray examination in March complete recovery seemed rather probable. But the April examination showed an extension to the left upper lobe. Weight was maintained through May 10th. X-ray then showed extension to both lungs: the animal lost weight rapidly, dyspnoea ensued, and death occurred on July 4, 1926, the 277th day after lung infection. Autopsy showed very extensive involvement of both lungs, but particularly of the right. The disease had massed peripherally under the pleura, which was as a covering of cheesy material and confluent cavities about a less involved central lung. The cavities were from 2 to 5 mm. in diameter, and occasionally even larger. The left lung showed a similar distribution, but to a lesser degree. The liver and spleen were macroscopically normal; kidneys were studded with tubercles

about 2 mm. in diameter. There was a slight nasal discharge, but no bony necrosis, and no acid-fast bacilli could be found.

Rabbit 13: Buck; 2721 gm. Received preliminary sensitization at same time and in same manner as rabbit 1. *August 24, 1925:* Intracutaneous test; good positive reaction (+++); retested September 29th, weak positive (+). *September 30:* Given intranasally 2 cc. of suspension containing 2.5 mgm. of virulent bovine bacilli.

October 5: X-ray examination on the fifth day after pulmonary infection showed dense cloudiness in middle half of right lung. Left lung normal.

October 15, 1925

R.: Increase of cloudiness throughout with exception of extreme base; homogeneous in character, suggesting pneumonia.

L.: Clear.

November 2: Losing weight in a surprising manner. Animal apparently quite well otherwise. On November 8th, found dead in morning without warning. Autopsy showed, in the right lung, involvement limited to middle and cephalic lobes. Lung parenchyma deeply congested, pneumonic, and speckled over its surface with discrete and confluent yellowish areas of caseation. Visceral pleura had lost its lustre; parietal pleura normal. Caudal lobe apparently normal. Left lung macroscopically normal. No cavity formation in either lung. Liver, spleen and kidneys macroscopically normal.

Rabbit 15: Buck; 2380 gm. Received preliminary sensitization at same time and in same manner as rabbit 1. *August 24, 1925:* Intracutaneous test gave weak positive reaction (+); retested September 28th, when negative. *September 30:* Given intranasally 2 cc. of suspension containing 2.5 mgm. of virulent bovine bacilli. *October 5:* X-ray examination showed diffuse mottling in the middle half of right lung; left lung clear.

October 15, 1925

R.: Increase of cloudiness in lower half.

L.: Clear.

October 26

R.: Probable clearing of some of collateral haze in lower half.

L.: Clear.

November 16

R.: Slight clearing of some of collateral haze in lower half.

L.: Clear.

December 14

R.: Clearing of cloudiness in lower half.

L.: Clear.

April 22, 1926

R.: Marked increase infiltration throughout.

L.: Decided increase infiltration throughout. Considerable fibrosis in both lungs.

Following the last X-ray examination of December 14th this rabbit was almost killed by others in the pen, and was used for other experiments. Both bovine bacilli and tuberculin were put into the right pleural cavity at times. The animal survived and was finally again X-rayed on April 22, 1926. Both lungs showed extensive involvement, but the left more markedly. Animal finally found dead on May 31, the 243rd day after pulmonary infection. At autopsy the right lung showed moderately extensive involvement, with confluent caseous areas, chiefly in the periphery of the lung. There were two cavities in the caudal lobe, about 2 mm. in diameter. The left lung was still more involved, particularly the caudal lobe, where there were two bleb-like cavities about 1 cm. in diameter and two cavities about 3 mm. in diameter. Liver, spleen and kidneys macroscopically normal.

Summary of Rabbits 9, 11, 13 and 15

These four rabbits were treated identically like rabbits 1, 3, 5 and 7, except that there was but one dose intranasally. They all showed an intense lung reaction on the fifth day after infection, going on to its maximum by the fifteenth or twenty-sixth day. Thereafter there was the same clearing in two of the rabbits as in the first four. Of the other two rabbits, one lived too short a time to show the clearing, and the other did not run true to form, in that the disease continued to progress after the initial reaction had spent itself.

None of these rabbits showed outward evidence of nasal disease. No definite relationship could here be made out between the intensity of the skin reaction and resistance to the pulmonary infection. Whereas rabbit 11 was the longest survivor, and had a ++++ and +++ reaction respectively on two occasions, rabbit 15 was + and negative respectively and was still relatively well protected.

The following four rabbits, nos. 10, 12, 14 and 16, served as control animals. They received no preliminary sensitizing dose of any sort, but simply the one dose intranasally.

Rabbit 10: Doe; 2721 gm. *September 30, 1925:* Given intranasally 2 cc. of the suspension containing 5 mgm. of dried virulent bovine bacilli. *October 5:* X-ray examination showed questionable fine mottling in lower half of right lung. Left lung was clear.

October 15, 1925

R.: Definite development or increase of mottling pretty much throughout.
L.: Questionable development of mottling in lower half.

October 26
R.: Mottling becoming more or less confluent; now homogeneous in character.
L.: General haziness in lower half.
November 16
R.: Definite and rather marked clearing of some of cloudiness in lower half.
L.: No definite evidence of any pathological change.
December 14
R.: Definite cavity formation, probably multilocular, in middle third.
L.: No definite changes.
January 18
R.: Cavity formation increased.
L.: No definite changes.
February 10
R.: Cavity formation increasing.
L.: No definite changes.
March 17
R.: Mottling increasing in lower half.
L.: Mottling developing in lower half.
April 22
R.: Increase of mottling throughout. Cavity formation larger.
L.: Decided increase infiltration throughout.

This animal showed by X-ray a slight but steady increase of its right-lung disease (October 26th and November 16th excepted). Nevertheless, its weight was maintained until March 22nd, when it was still 3174 gm. From then on there was a rapid fall, concomitant with a striking increase in X-ray shadows in the lungs. On May 10th, weight was only 2097 gm. The animal found dead on May 15th, the 227th day after lung infection. Autopsy showed right upper-lobe tissue replaced by multilocular cavity formation. The remainder of the lung was practically consolidated with confluent tubercles; but the lesions were distinctly more dense under the pleura. The left lung was devoid of cavities, but was otherwise like the right, except for a lesser degree of involvement. Again there was a subpleural massing of infection.

Rabbit 12: Buck; 2480 gm. Smaller and more delicate than most of the other animals. *September 30, 1925:* Given intranasally 2 cc. of suspension containing 5 mgm. of virulent bovine tubercle bacilli. *October 5:* X-ray examination shows some mottling in lower half of right lung. Left lung clear.

October 15, 1925
R.: Increase of mottling in lower two-thirds.
L.: Development of mottling in lower half.
October 26
R.: Increase of mottling, now more or less homogeneous or pneumonic.
L.: Increase of mottling, very dense in areas.
November 16
R.: Mottling extending toward base.
L.: Cavity formation apparently developing in middle third.

December 14
R.: No definite changes in shadows previously mentioned.
L.: No definite changes in shadows previously mentioned.
January 18, 1926
R.: Multilocular cavity formation in middle third.
L.: Multilocular cavity formation in middle third.

This rabbit maintained its weight up to January 11, 1926, when it began to lose. Found dead on January 29th, the 121st day after pulmonary infection.

Autopsy: Right lung about one-third larger than the left. A few fine, easily broken adhesions over right upper lobe and attaching lower lobe to diaphragm. Whole right lung extensively involved with gelatinous and caseous pneumonia. In the cephalic lobe was a large cavity, about 1.5 cm. in diameter and with a thin parchment-like wall projecting into the interlobar fissure. There were also three other cavities in the right cephalic lobe, the largest about 0.75 cm. in diameter. *Left lung:* no cavity formation; otherwise similar to right, but less extensively diseased.

Rabbit 14: Doe; 3174 gm. *September 30, 1925:* Given intranasally 2 cc. of suspension containing 2.5 mgm. of virulent bovine bacilli. *October 5:* X-ray examination shows no shadow in either the right or left lung.

October 26, 1925
R.: Development of marked cloudiness more or less throughout. Pneumonia.
L.: Clear.
November 16
R.: Possible clearing of some of cloudiness near base.
L.: Clear.
December 14
R.: Continued clearing of some of cloudiness in lower half.
L.: Clear.
January 18, 1926
R.: Multilocular cavity formation in upper two-thirds. Increase of mottling in lower half.
L.: Development of mottling in lower half.
February 10
R.: Increase of mottling pretty much throughout.
L.: Increase of mottling pretty much throughout.

This animal did not begin to lose weight until January 29, 1926. On February 20th, still weighed 2721 gm. Found dead February 24th.

Autopsy: Lungs showed very extensive involvement on both sides, but particularly on the right. The right cephalic lobe was consolidated, with yellow cheesy areas visible at a number of points. In this and in the middle lobe were multilocular cavities, bleb-like in the thinness and transparency of their walls. They were about 0.5 to 1 cm. in diameter. The remainder of the right lung, and the left lung were extensively involved, with considerable

fibrosis, but not much caseation. The heart was pushed into the left hemithorax by the enlarged right cephalic lobe. There was no adhesive pleurisy, and no cavity formation in the left lung. Liver and spleen macroscopically normal. Both kidneys showed a few small white semi-fibrous areas on the surface.

Rabbit 16: Buck; 1331 gm. This rabbit was only half the size of the larger rabbits. *September 30, 1925:* Given intranasally 2 cc. of suspension containing 2.5 mgm. of virulent bovine bacilli (strain B1). *October 5th:* X-ray examination: neither lung shows any cloudiness.

October 15, 1925
R.: Development of marked cloudiness pretty much throughout.
L.: Clear.
October 26
R.: Dense cloudiness pretty much throughout.
L.: Clear.
November 16
R.: Increase in intensity of mottling in lower half.
L.: Development of mottling in middle third.
December 14
R.: Probable cavity formation developing in middle third.
L.: Development of mottling throughout. Suggestion of cavity formation in upper third.

This rabbit increased in weight, and was evidently young and still growing. Weight at death, 1814 gm. On December 27th was found dead, the 88th day after pulmonary infection. Both lungs showed very extensive disease, with multilocular cavity formation in the upper half of right lung. No cavity formation in the left lung.

Summary of Rabbits 10, 12, 14 and 16

In all four of these rabbits there was little or nothing to be seen on X-ray examination on the fifth day after pulmonary infection; indeed, nothing whatever in two of the animals. In three of the rabbits there was progressive increase of disease, as shown by X-ray films, and no tendency to clearing after the height of the pneumonic reaction had been reached; in the fourth, no. 10, there was clearing until cavity formation developed during the third month. Thereafter there was steady increase of disease until death occurred. Cavity formation of considerable extent occurred in all of these animals, usually definite or suggested in the X-ray films of the third month. Once it was observed on the twenty-seventh day.

DISCUSSION

These experiments bear out the experience of Mullin and Ryder (1), Corper and Robin (2), Corper (3), Whipple (4), Lemon (5) and others, as to the ease and apparently unhindered manner in which fluids, injected into the upper respiratory passages of animals,—particularly when anaesthetized,—flow through the larynx into the lungs. Not a single animal of the twelve failed of severe lung infection, and while the whole of the instilled suspension did not necessarily enter the lung, there was no evidence in any case to suggest that any large amount had escaped into the stomach. As one would have expected from the experience of the above-cited authors, the suspension flowed almost entirely into the dependent lung, which, in our experiments, was always the right; and it was usually the cephalic lobe which received the first and heaviest infection. This localization is in all probability due to gravity and aspiratory suction: with the animal lying upon its side the material enters most readily into the cephalic-lobe bronchus.

Caudal-lobe disease was usually the result of extension from elsewhere. There was no evidence that dissemination occurred earlier in the control than in the superinfected animals, or *vice versa*. In each set there were animals in which the disease moved early to the left lung, and others in which it remained localized to the right for relatively long periods. It was found, however, that, when spread to the left lung did occur, it was generally to the caudal part. Of 8 animals in which this point could be determined, 5 showed the first extension into the caudal half, 2 into the middle of the lung, and only one into the cephalic half of the good lung.

After the disease became chronic and more or less generalized in the right lung, it was found to have massed itself underneath the pleura especially. In 4 of 7 rabbits, in which this point was determinable, there was on lung-section a definite margin or frame of caseous material surrounding an area much less involved. In the case of rabbit 11 the caseous periphery had been expelled and the lung-section presented a border of small, confluent and discrete cavities about a less diseased centre.

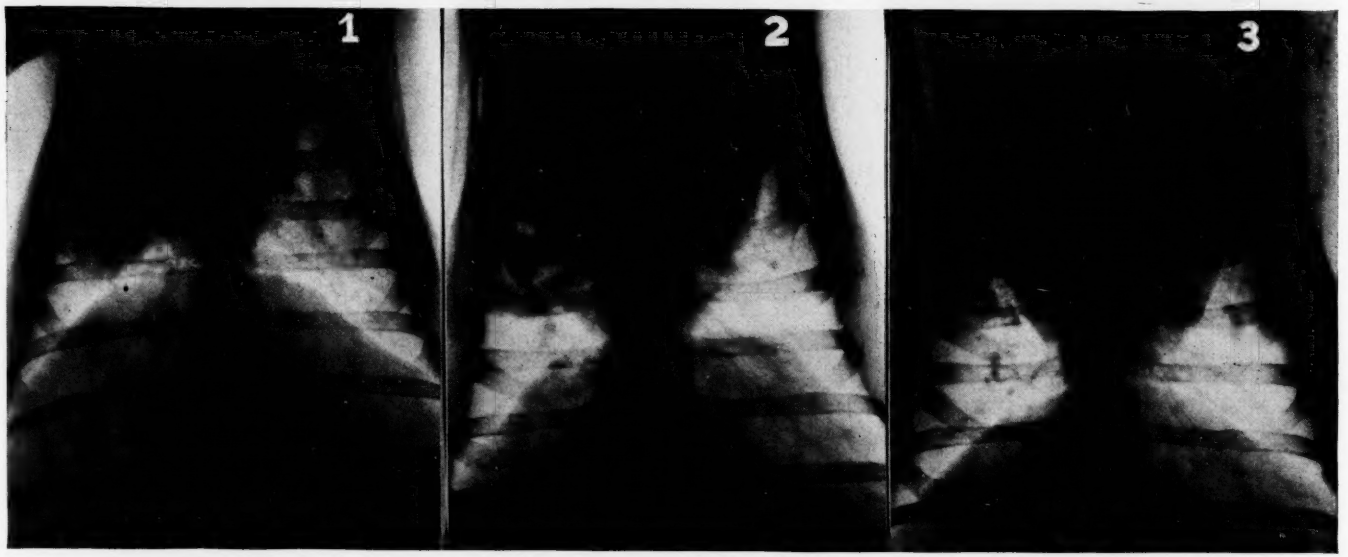
Adhesions occurred surprisingly seldom, considering the amount of tuberculosis in the lungs and the duration of survival of several of the animals. Of 7 superinfected rabbits only 2 showed any adhesive pleurisy whatever. In no. 3 the whole right lung was tightly bound to

the chest-wall and diaphragm; in no. 15 there were a few soft adhesions at two or three points. Only one of the 4 control rabbits exhibited adhesions, which were thin and few in number. The earlier deaths of the controls may account for this.

As has been observed by several experimenters, the reaction to superinfection was both earlier and more intense than that to the primary infection. In none of the control rabbits was there any marked reaction by the fifth day, and 2 of the 4 showed even then no shadow whatever in the X-ray films. Rabbits 9, 11, 13 and 15, which may properly be compared with the controls, reacted more quickly and more violently; by the fifth day two of them already showed dense consolidation, while in the other two there was a considerable shadow. In the subsequent films of October 15th and 26th, the superinfected animals maintained their lead.

Rabbits 1, 3, 5 and 7 were particularly interesting in this respect. The first small superinfecting dose of 0.5 or 1 mgm. produced little or no lesion within nineteen days. When, however, there was added in the lung a further superinfecting dose of 2.5 or 5 mgm., the reaction at the end of another seven days was very marked indeed. It would not seem that the small, first superinfecting dose had taken on virulence or multiplied during the fifth week to the extent of being a large factor in the extensive reaction found one week after the second dose into the lung; rather it would appear that the lungs were rendered still more sensitive by the infection already existing in the lung. Philibert and Cordey (6) consider that rabbits, sensitized by infection of the lung instead of the skin, become more susceptible to pulmonary superinfection and suffer more extensive disease and worse effects than do unsensitized controls. While our 4 animals showed such a marked reaction after the second superinfecting dose into the lung, they, nevertheless, cleared up this inflammation to a considerable degree, and survived just as long as superinfected rabbits 9, 11, 13 and 15, which received only one infection into the lung. Furthermore, no cavities were found in these animals, although no. 3 showed a cheesy mass in the right caudal lobe which would probably have been expelled in a short time.

Perhaps the most interesting development of all was the very marked clearing of the dense consolidation observed early in the superinfected animals. One rabbit, no. 13, died too early to exhibit this phenomenon, but in 6 of the remaining 7 superinfected rabbits clearing took place, and in some animals (see figures 1, 2 and 3 of rabbit 3 and figures 4, 5



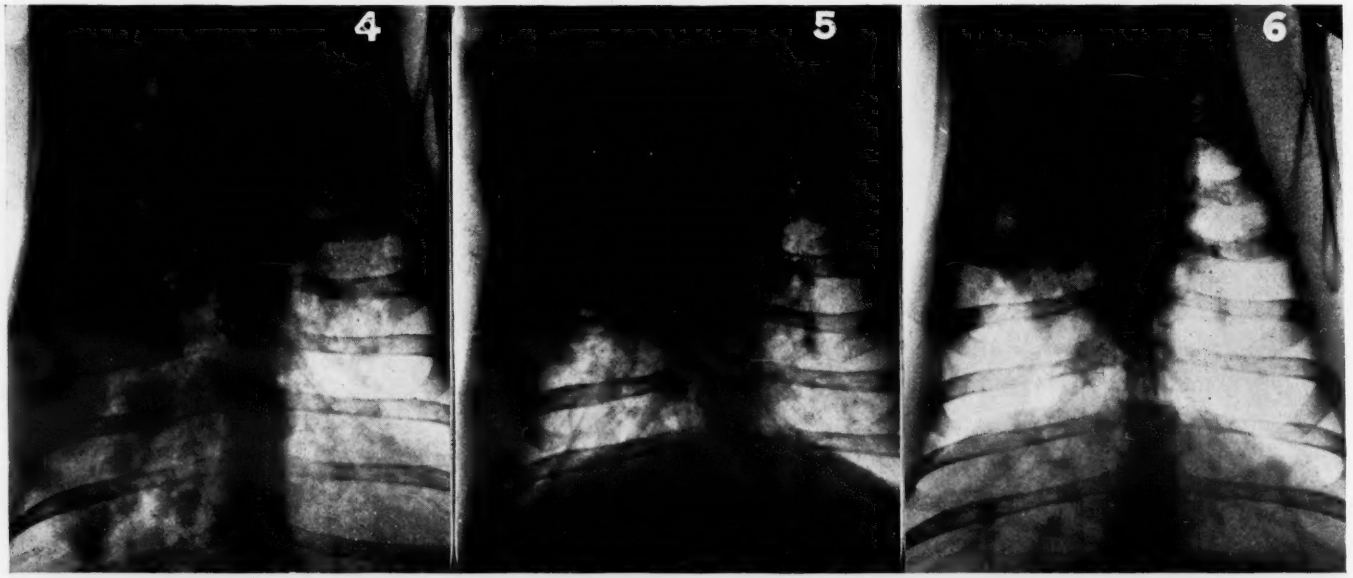
RABBIT 3: TO SHOW CLEARING

Human tubercle bacilli subcutaneously, August 4. Bovine tubercle bacilli, 1 mgm. intrapulmonary, August 28. Bovine bacilli, 5 mgm. intrapulmonary, September 17

FIG. 1. FILM TAKEN SEPTEMBER 24TH, 7 DAYS AFTER SECOND PULMONARY SUPERINFECTION. HEAVY INFILTRATION IN RIGHT UPPER LOBE. NOTE ABSENCE OF HEART OUTLINE, AS A RESULT OF PULMONARY SHADOW.

FIG. 2. FILM TAKEN OCTOBER 26TH, 39 DAYS AFTER SECOND PULMONARY SUPERINFECTION. DECIDED CLEARING OF MUCH OF THE CLOUDINESS IN RIGHT UPPER LOBE. NOTE ALMOST COMPLETE REËSTABLISHMENT OF HEART OUTLINE.

FIG. 3. NOVEMBER 16TH, 60 DAYS AFTER SECOND PULMONARY INFECTION. CLEARING CONTINUES, AND UPPER LOBE THROUGHOUT IS QUITE CLEAR. NOTE PARTICULARLY THE COMPLETE REËSTABLISHMENT OF HEART OUTLINE.



RABBIT 11: TO SHOW CLEARING

Human tubercle bacilli subcutaneously August 4. Bovine tubercle bacilli, 5 mgm. intrapulmonary, September 30

FIG. 4. FILM TAKEN OCTOBER 26TH, 26 DAYS AFTER PULMONARY SUPERINFECTION. DECIDED MOTTLING THROUGHOUT THE RIGHT LUNG. SLIGHT MOTTLING IN LEFT LUNG.

FIG. 5. FILM TAKEN FEBRUARY 10TH, 135 DAYS AFTER PULMONARY SUPERINFECTION. DECIDED CLEARING OF MOTTLING IN LOWER HALF OF RIGHT LUNG.

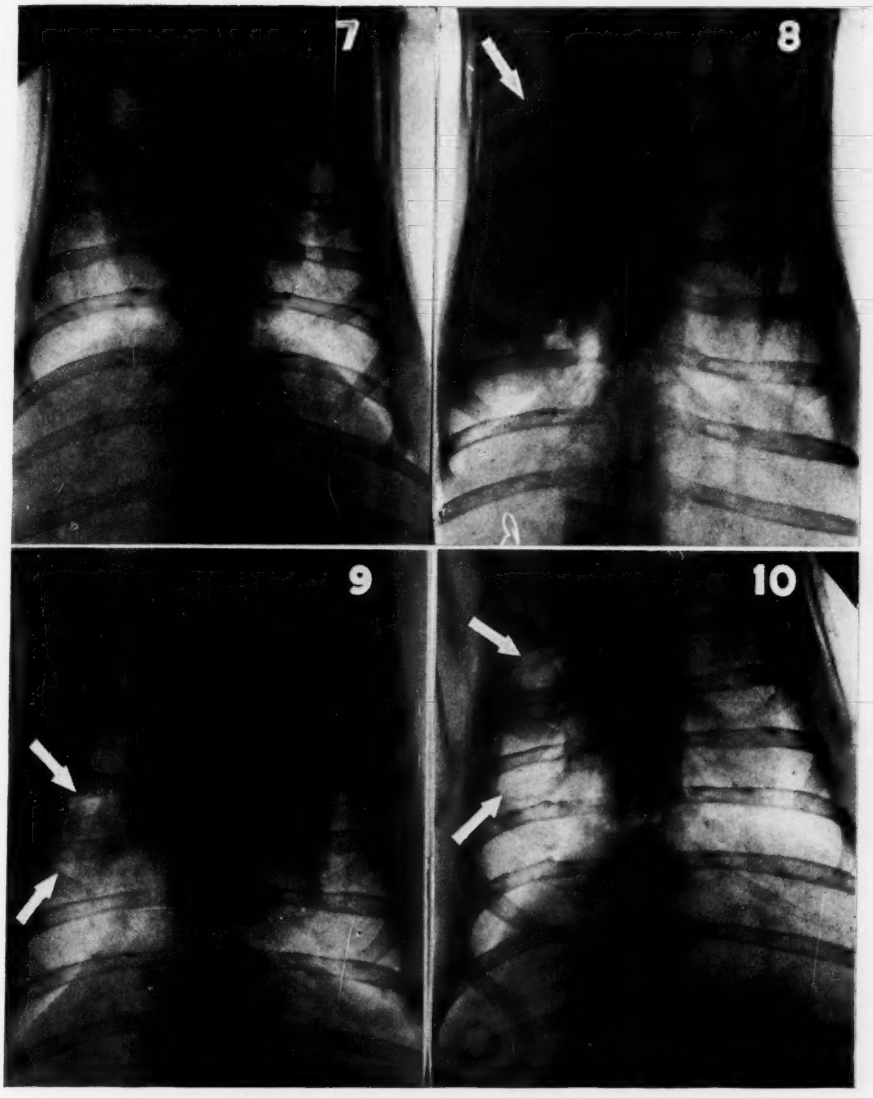
FIG. 6. FILM TAKEN MARCH 17TH, 168 DAYS AFTER PULMONARY SUPERINFECTION. PRONOUNCED CLEARING OF MOTTLING THROUGHOUT LOWER PORTION OF RIGHT LUNG. ALMOST COMPLETE REËSTABLISHMENT OF HEART OUTLINE AS RESULT OF CLEARING. LEFT LUNG RELATIVELY CLEAR.

and 6 of rabbit 11) was most marked, not only as observed over a longer period, but even from month to month. Such an absorption of tuberculous pneumonic tissue, or collateral inflammation, has been often described of late, particularly since Gardner's work (7), and is now widely recognized by specialists in tuberculosis, though not appreciated generally outside that group.

As to cavity-formation, it occurred uniformly in the 4 control rabbits, in which infection was primary. X-ray films showed it on the 75th, 47th, 110th and 75th days, respectively, after infection. All of the observations were later confirmed by autopsy. Cavitation, too, was quite extensive and multilocular. It was usually the forerunner of accelerated decline and was always followed by a spread, as revealed in the next X-ray examination. In contrast to the control rabbits, and to our surprise, there was much less tendency to cavity-formation in the superinfected animals. Of the 8 superinfected rabbits there were only two which at autopsy showed any cavity-formation, namely, nos. 11 and 15. In both of them there were fairly extensive antra, for the most part just underneath the visceral pleura. There is good reason to believe that the time-element is very essential for cavity-formation in the superinfected rabbits, since rabbits 11 and 15 were the longest survivors, 277 and 243 days respectively, and neither of them showed a suggestion of cavities in the last X-ray films, taken approximately two months before death. In considering the superinfected rabbits which died earlier, without cavity-formation but with marked caseation, one had the impression that cavity-formation would necessarily have had to follow in time. Figures 7, 8, 9 and 10 of rabbit 10 show the gradual development of cavity formation in one of the control animals.

The dosage or amount of bacilli given for superinfection is a very important factor in the degree of reaction. Whereas, in two rabbits 1 mgm. of bovine bacilli, and in two others 0.5 mgm., failed to produce within nineteen days lesions more than barely visible by X-ray, five times these amounts, or 5 and 2.5 mgm., produced very extensive pneumonic lesions within fifteen days. As between the reactions to 5 and 2.5 mgm. no clean-cut difference was evident, although slight inequalities with more extensive lesions due to the 5 mgm. did occur here and there.

With all of the 8 superinfected rabbits an attempt was made to determine what relation, if any, existed between the intensity of the intracutaneous reaction to tuberculin, on the one hand, and the intensity of



RABBIT 10: TO SHOW CAVITY-FORMATION

Single pulmonary infection, September 30th

FIG. 7. FILM TAKEN OCTOBER 5TH, 5 DAYS AFTER PULMONARY INFECTION. QUESTIONABLE CLOUDING IN RIGHT UPPER LOBE

FIG. 8. FILM TAKEN OCTOBER 26TH, 26 DAYS AFTER PULMONARY INFECTION. HEAVY INFILTRATION IN RIGHT UPPER LOBE, INDICATED BY ARROW. HAZINESS ON LEFT SIDE DUE TO HEART BEING THROWN ALMOST COMPLETELY INTO LEFT THORAX

FIG. 9. FILM TAKEN DECEMBER 24TH, 85 DAYS AFTER PULMONARY INFECTION. CAVITIES INDICATED BY ARROWS. SHADOW DENSITY LESS MARKED, PROBABLY DUE TO CAVITY DEVELOPMENT PLUS SOME CLEARING

FIG. 10. FILM TAKEN FEBRUARY 10TH, 133 DAYS AFTER PULMONARY INFECTION. CAVITIES GREATLY ENLARGED, INDICATED BY ARROWS. HAZINESS ON LEFT SIDE DUE TO HEART SHADOW

the pulmonary reaction to superinfection, and prognosis, on the other. Animals 1, 3, 5 and 7 reacted to 0.1 cc. of 10 per cent O. T. intracutaneously four plus, one plus, three plus and two plus, respectively, four days before their first superinfecting dose into the lung. There was no apparent difference in reaction in the X-ray films. Also, the animals survived 209, 208, 279 and 161 days, respectively. The animal which survived the longest had a three-plus reaction, while the shortest-lived animal had two plus. No. 3, with only a one-plus skin reaction, lived 208 days. Rabbits 9, 11, 13 and 15 reacted three plus, three plus, one plus and negative just before superinfection into the lung. Again, the X-ray films showed no apparent difference in reaction to lung infection, and there seemed to be no relationship between the period of survival and the intensity of the intracutaneous test.

A quite striking feature in this work was the increase in volume of the diseased lung. Unfortunately, it struck our attention too late for the diseased lungs to be compared in weight and volume with normal lungs of rabbits of the same size, and it can only be given here as a simple statement that the affected lungs were relatively much enlarged; the more the tuberculous disease the greater the lung volume. This fact, in the rabbit at least, would seem to be of considerable interest as affecting the position of the lung fissures and margins.

In an earlier paper, on tuberculous superinfection of the meninges in the rabbit (8), we called attention to the changes in the animals' weight. In the experiments there reported the weight maintained itself practically unchanged over a considerable period, during which the rabbit successfully combated its meningitis. When, at a given time the weight did begin to fall, it continued to decrease, and meningeal symptoms were never slow to set in. In the control animals, however, in which the intrameningeal infection was primary and the meningitis progressive from the outset, the loss of weight was practically continuous from the infection to death.

In superinfection of the rabbit's lung the weight apparently behaves in the same manner. Infection is present and in large amount, as shown by the X-ray, but the weight is maintained, or even increased, over a period of months in some animals. But, with the dosage which we employed, a time always came when the weight began to fall, and then continued to go down until the animal's death. As a rule this more or less sudden change of weight was coincident with an extensive spread of disease as shown by the X-ray. In the pulmonary infections, how-

ever, contrary to our experience with meningeal infection, the control rabbits also maintained their weight, often for a considerable time, before showing the loss which always presaged death. In them also the X-ray showed rapidly progressive disease from the time that the weight began to decrease rapidly. Summaries of weights are given in the protocols appearing earlier in the article. The weights of two rabbits will here be given in detail:

Rabbit 1: Superinfected intranasally August 28, 1925, and September 17, 1925. September 12th, 2777 gm.; October 1st, 2919 gm.; October 13th, 3004 gm.; October 20th, 2890 gm.; November 2nd, 2919 gm.; November 9th, 2919 gm.; November 18th, 3316 gm.; December 2nd, 3287 gm.; January 5, 1926, 3287 gm.; February 8th, 3004 gm.; March 3rd, 2947 gm.; March 11th, 2777 gm.; March 22nd, 2493 gm.; April 8th, 2069 gm.; April 14th, death. In this animal the films of February 12th showed some increase of disease as compared with those of January 18th, but it was in those of March 17th that the extension was markedly visible.

Rabbit 14, Control: Primary infection intranasally September 30, 1925, 3174 gm.; October 1st, 2947 gm.; October 26th, 3004 gm.; November 2nd, 2834 gm.; November 6th, 2862 gm.; November 18th, 3145 gm.; December 2nd, 3117 gm.; December 14th, 3032 gm.; January 5, 1926, 3060 gm.; January 19th, 2947 gm.; January 26th, 2805; February 8th, 2749 gm.; February 20th, 2721 gm.; February 24th, death. Here the very striking change in the films was between those of December 14th and January 18th.

Philibert and Cordey (6) in 1925 reported results not unlike ours. Among other experiments they inoculated one group of rabbits subcutaneously with human tubercle bacilli, and later superinfected them intratracheally with 1 to 5 cgm. of human bacilli. The rabbits were killed twenty-six days after intratracheal superinfection. The lesions were more extensive and diffuse than in the guinea pig, and appeared to have less tendency to caseation. On the contrary, they tended to hyperplasia, ending in massive hypertrophy of the lung. In another groups of rabbits, large amounts of human bacilli (5 and 10 cgm.) were given intratracheally, both as primary and superinfecting doses. Very intense congestions were often produced, but only exceptionally in the animals infected primarily. The lesions were most often proportional to the total dosage, as much to that of the first as to that of the second infection. Massive caseous areas, with production of large cavities, took place in 2 of 5 superinfected rabbits.

Our own superinfected animals, about three weeks after the pulmonary infection, showed by X-ray a very extensive involvement, which would correspond with the rabbits of Philibert and Cordey killed on the 26th day. But there was no suggestion of cavity-formation at that time, and all but one of the animals cleared up a considerable portion of the collateral pneumonic process before going into chronic dis-

ease. It was probably the much larger dosage used by the French workers which produced the more severe effect.

CONCLUSIONS

1. The method of pulmonary infection by the instillation of a suspension of tubercle bacilli into one nostril of the anaesthetized rabbit affords a very simple method of producing tuberculosis of one lung. The localization of the infection is determined chiefly by gravity, the position of the animal being the important factor. The possibility of infection of the nares must be borne in mind.

2. X-ray films afford an excellent means of studying the development and progress of pulmonary tuberculosis in the rabbit, and should be more generally employed.

3. An early pneumonic reaction to aspiration of virulent tubercle bacilli may occur in the lungs of both sensitized and normal rabbits. It is more immediate, more intense and more constant in the sensitized animals.

4. Of the different factors which determine the degree of early reaction to tubercle bacilli in the sensitized lung, the quantity of bacilli introduced is a very important one.

5. The initial pneumonic reaction may undergo almost complete resolution in both sensitized and normal rabbits. Resolution is more rapid, more complete and more constant in the sensitized animals.

6. Cavities form in both sensitized and normal rabbits, but more rapidly and more extensively in the normal animals.

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A SENSITIZATION METHOD OF DIFFERENTIATING AVIAN FROM MAMMALIAN TUBERCLE BACILLI

A. B. CRAWFORD[1]

The differentiation of the avian type of tubercle bacillus from the human and bovine types can, in a great majority of cases, be definitely made by established methods. In some instances, however, difficulty is encountered with atypical and avirulent strains. One such instance was recently experienced in connection with the Calmette *BCG* tubercle bacillus. This microörganism is described by Calmette as being a bovine tubercle bacillus which, during the course of many years' cultivation on bile-potato medium, has lost its power to produce lesions of tuberculosis. Tests are being made at the Experiment Station of the immunizing properties of the *BCG* bacillus and in this connection it was deemed desirable to show that the culture in our possession was not an attenuated tubercle bacillus of the avian type. The animal-inoculation method of differentiation obviously could not be used, because it had already been proved that the *BCG* bacillus was innocuous for all species of animals, including fowls, into which it had been inoculated.

A method was devised for use in this connection, which is based on the specificity of the sensitization caused by avian and mammalian tubercle bacilli to avian and mammalian tuberculins, respectively. This is termed *the sensitization method of differentiation.* It is common knowledge that guinea pigs affected with mammalian tuberculosis manifest a very marked hypersensitiveness to mammalian tuberculin, while a relatively slight sensitiveness is manifested toward avian tuberculin. With guinea pigs sensitized by avian tubercle bacilli, however, reactions are obtained at times with both kinds of tuberculin, but in every instance avian tuberculin produces the more marked reaction.

TECHNIQUE

The technique followed in typing the *BCG* bacillus was as follows: Fifteen guinea pigs, averaging 450 gm. in weight, were inoculated

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intraäbdominally each with 5 mgm. of *BCG* culture, moist weight, suspended in 1 cc. of Ringer's solution. After thirty days, 5 of these guinea pigs were injected intraäbdominally, each with 2 cc. of avian tuberculin per 500 gm. weight; 5 were injected intraäbdominally, each with 2 cc. of mammalian tuberculin per 500 gm. weight; and the remaining 5 were injected intracutaneously, each with 0.1 cc. avian tuberculin and 0.1 cc. mammalian tuberculin, the avian tuberculin being injected into the skin on one side of the abdomen and the mammalian tuberculin on the opposite side.

DESCRIPTION OF TUBERCULINS

The tuberculins used in these tests were prepared in the Biochemic Division of the Bureau of Animal Industry. Each cubic centimetre used in intraäbdominal injections contained the equivalent of 0.125 gm. of Koch's O. T. and each cubic centimetre of intracutaneous tuberculin contained the equivalent of 0.25 gm. of O. T.

The mammalian tuberculin was prepared from a human strain of the tubercle bacillus.

Bovine tuberculin was not used in these tests. The inclusion of bovine-tuberculin groups would have added greatly to the labor and cost of the experiment without adding proportionately to its value, since animals sensitized by either bovine or human tubercle bacilli react equally well to both bovine and human tuberculin.

RESULTS WITH *BCG*

Both the intraäbdominal and intracutaneous injections of mammalian tuberculin caused the manifestation of specific tuberculin reactions, while no reaction to either type of injection was elicited by avian tuberculin.

Of the group of 5 guinea pigs receiving intraäbdominal injections of avian tuberculin, none showed a systemic reaction (table 1). Of the 5 injected with mammalian tuberculin, 2 died within twenty-four hours and one after twenty-four hours, and the other 2 showed well-marked reactions but recovered.

The results of the cutaneous tests are shown in table 2.

APPLICATION OF METHOD TO KNOWN STRAINS

In order to show that the sensitization produced by avian and mammalian types of tubercle bacilli is specific, to a diagnostic degree, to avian and mammalian tuberculins, respectively, the technique described above was applied to four avian, three bovine, and one human strain.

The avian strains used were the Experiment-Station strain, Pathological-Division strain, Biochemic-Division strain, and Prague strain. Inoculations were made intraäbdominally, each guinea pig receiving an injection of 5 mgm. of culture, moist weight, suspended in 1 cc. of Ringer's solution.

The bovine strains used were nos. 642, 854 and 1,094, all of which were isolated from lesions in cattle. They have been grown on culture media many years and have been proved, culturally and by animal inoculation, to be true bovine strains. Inoculations were made subcutaneously, on the inner surface of the right thigh, and the dose of inoculum for each guinea pig was about 0.01 mgm., moist weight, suspended in 0.5 cc. of Ringer's solution.

The human strain was obtained over five years ago from the Biochemic Division, where it had been under artificial cultivation for many years. Inoculation was made intraperitoneally, each guinea pig receiving an injection of 0.25 mgm. suspended in 1 cc. of Ringer's solution.

RESULTS WITH KNOWN STRAINS

1. Avian Type: Biochemic-Division Strain

Systemic Reactions: The intraperitoneal injection of avian tuberculin caused the death of one animal within twenty-four hours, three after twenty-four hours, and the remaining animal showed a slight reaction. Mammalian tuberculin caused the death of one guinea pig after the twenty-fourth hour and the remaining 4 showed no reaction (table 1).

Cutaneous Reactions: In each of the 4 guinea pigs tested, avian tuberculin produced typical reactions, ranging from 15 to 25 mm. in diameter; mammalian tuberculin caused very little reaction, the manifestations being characterized principally by a slight thickening of the skin (table 3).

2. Avian Type: Pathological-Division Strain

Systemic Reactions: The intraperitoneal injection of avian tuberculin caused the death of 3 guinea pigs within twenty-four hours, and the

remaining 2 died after the twenty-fourth hour; mammalian tuberculin caused the death of one guinea pig, one showed a well marked reaction but recovered, and the other 3 only slight reactions (table 1).

Cutaneous Reactions: Avian tuberculin produced extensive typical reactions, ranging in size from 20 to 30 mm. in diameter; none of the reactions to mammalian tuberculin were typical (table 4).

3. Avian Type: Prague Strain

Systemic Reactions: The intraperitoneal injection of avian tuberculin caused the death of 2 guinea pigs within twenty-four hours, one after twenty-four hours, and the remaining 2 animals showed slight reactions but recovered. Mammalian tuberculin caused the death of one guinea pig within twenty-four hours, one after twenty-four hours, one showed a slight reaction but recovered, and the other 2 showed no reaction (table 1).

Cutaneous Reactions: Both tuberculins produced characteristic tuberculin reactions, the only difference being that avian tuberculin invariably produced a reaction from one and one-half to four times the diameter of the reaction caused by mammalian tuberculin (table 5).

4. Avian Type: Experiment-Station Strain

Systemic Reactions: The intraperitoneal injection of avian tuberculin caused the death of one guinea pig within twenty-four hours, and of 2 after twenty-four hours; of the 2 remaining, one showed a well-marked reaction and the other a slight reaction, both recovering. The mammalian tuberculin caused the death of one guinea pig after twenty-four hours, one showed a well-marked reaction, 2 slight reactions, and the remaining animal showed no reaction (table 1).

Cutaneous Reactions: Avian tuberculin, applied intracutaneously, produced characteristic reactions, ranging in size from 1 to 3.5 cm. in diameter. With mammalian tuberculin, 3 of the guinea pigs manifested atypical reactions, while the other 2 animals had reactions practically identical in appearance to the corresponding avian tuberculin reactions except that they were smaller in size (table 6).

5. Bovine Type: Strain 1,094

Systemic Reactions: The intraperitoneal injection of avian tuberculin produced no reaction; mammalian tuberculin killed all 5 guinea pigs within twenty-four hours (table 1).

Cutaneous Reactions: Of the 5 guinea pigs receiving intracutaneous injections of avian tuberculin, 2 showed fairly typical but small reactions, 2 atypical reactions, and one no reaction; the reactions to mammalian tuberculin were very pronounced, especially in the 2 animals which had positive reactions to avian tuberculin (table 7).

6. Bovine Type: Strain 854

Systemic Reactions: The 5 guinea pigs receiving intraperitoneal injections of avian tuberculin showed only slight reactions; of the 5 receiving mammalian tuberculin, 2 died within twenty-four hours and the other 3 after twenty-four hours (table 1).

Cutaneous Reactions: There was practically no reaction to avian tuberculin, while each guinea pig showed an extensive reaction to mammalian tuberculin (table 8).

7. Bovine Type: Strain 642

Systemic Reactions: None of the guinea pigs receiving intraperitoneal injections of avian tuberculin showed a systemic reaction. Of the 5 guinea pigs receiving injections of mammalian tuberculin, one died within twenty-four hours, 2 after twenty-four hours, and the remaining two showed well-marked reactions but recovered (table 1).

Cutaneous Reactions: None of the 4 guinea pigs receiving intracutaneous injections of avian tuberculin showed typical reactions. All 4, however, showed marked reactions to mammalian tuberculin (table 9).

8. Human Type: Biochemic-Division Strain

Systemic Reactions: Each of the 5 guinea pigs receiving intraperitoneal injections of avian tuberculin showed a well-marked systemic reaction but recovered. All 5 guinea pigs receiving mammalian tuberculin died within twenty-four hours (table 1).

Cutaneous Reactions: Each of the 5 guinea pigs receiving an intracutaneous injection of avian tuberculin showed a diffuse swelling at the site of injection, but none manifested the characteristic type of reaction observed on the opposite side where mammalian tuberculin was injected. All the responses to mammalian tuberculin were very extensive (table 10).

TEST OF FRIEDMANN TURTLE BACILLUS

In another investigation (1), in which the same technique was used, a test was made of the hypersensitiveness produced in guinea pigs by various acid-fast microörganisms, among which was the so called *Friedmann turtle bacillus*. The test of this microörganism is of interest, as it is believed to be of possible human origin.[2] In guinea pigs, sensitized by the Friedmann turtle acid-fast bacillus, systemic reactions were not obtained with either avian or mammalian tuberculin. The reactions to the intracutaneous injections of both tuberculins were negative in a majority of the guinea pigs, and in the others resulted in only a slight thickening of the skin. Practically similar results were obtained in the test of another acid-fast microörganism bearing the name of *Fish bacillus*. It would appear from this test that the Friedmann turtle bacillus was not of human origin.

DISCUSSION

White guinea pigs were chosen for the cutaneous tests because reactions are more discernible in this type. It was not found that white guinea pigs were better sensitized than mixed-colored guinea pigs.

Reactions caused by mammalian tuberculin in guinea pigs sensitized by mammalian tubercle bacilli, and avian tuberculin in guinea pigs sensitized by avian tubercle bacilli will be referred to as specific reactions; reactions caused by mammalian tuberculin in guinea pigs sensitized by avian tubercle bacilli, and by avian tuberculin in guinea pigs sensitized by mammalian tubercle bacilli, will be referred to as nonspecific reactions.

The cutaneous reactions were observed at the 24th, 48th, and 72nd hours. At the 24th hour, reactions, as a whole, were diffuse and poorly defined; at the 48th hour, the optimum for observations, reactions had reached their maximum in intensity and definition; and at the 72nd hour resolution had set in. Occasionally the nonspecific reaction at the 24th hour would be only slightly smaller than the specific reaction, whereas at the 48th hour there would invariably be a marked difference, the nonspecific reaction tending to resolve while the specific reaction

[2] In Hiss and Zinsser's *Text Book of Bacteriology, p. 616*, it is stated, "As a possible human origin for the turtle infections Friedmann mentions that the attendant who fed these turtles suffered from a double pulmonary tuberculosis."

became better developed. This was especially true in the groups sensitized by avian tubercle bacilli.

In the guinea pigs sensitized by virulent mammalian tubercle bacilli, the degree of sensitization generally paralleled the extent of the lesions, and the variation in the lesions at a definite period was associated with the difference in virulence of the sensitizing microörganisms, the other factors, such as method of inoculation, size of dose, etc., being uniform.

In guinea pigs, sensitized by avian or by avirulent mammalian tubercle bacilli, the degree of sensitization seems to depend on the quantity of bacilli injected. The intraäbdominal injection of not more than five mgm. of avian tubercle bacilli leads to the formation of nonprogressive lesions, which are quite similar in appearance to lesions caused by avirulent and killed mammalian tubercle bacilli, namely, a thickening and induration of the omentum in which are found from one to six tubercles, ranging in size up to 5 mm. and adhesions between the peritoneum and viscera. Occasionally, this dose causes a slightly enlarged, smooth spleen and small areas of coagulation necrosis in the liver. In every instance, the intraperitoneal injection of 5 mgm. of culture led to a satisfactory degree of sensitization.

Another point observed was that mammalian tuberculin appeared to be a better agent for detecting avian tubercle-bacillus sensitization than was avian tuberculin in detecting mammalian tubercle bacillus sensitization. In the systemic-reaction groups, mammalian tuberculin caused the death of at least one guinea pig in each of the groups sensitized by avian tubercle bacilli, while avian tuberculin caused no deaths and only slight reactions in the mammalian sensitized groups, with the exception of the group sensitized by the human strain. In this case, however, it is surprising that some of the animals did not die, as the lesions were very extensive. Inasmuch as this microörganism had beeen grown continuously on culture medium for many years and no test had been made of its virulence, it was felt that a relatively large dose, injected intraperitoneally, would be necessary to cause a satisfactory sensitization. On the 29th day, when the tuberculin injections were made, the guinea pigs had fallen off considerably in weight, and on postmortem examination each showed extensive lesions of tuberculosis in the liver, spleen, omentum and abdominal lymph nodes. Each of the group of 5, which received mammalian tuberculin intraperitoneally, was dead when observed sixteen hours after injection, and all appeared at that time to have been dead for several hours.

The intracutaneous test appears to be a more delicate test of sensitization than the systemic test. This was observed not only in this experiment but in another investigation, in which the sensitization caused by various acid-fast microörganisms other than tubercle bacilli was studied (1). The specific reactions elicited by the intracutaneous test were invariably well-marked and constant. The nonspecific reactions, however, were inconstant. In the latter, two variables were observed: (1) a difference in the sensitizing properties of the different strains, and (2) a difference in the sensitization of individual guinea pigs of the same group. Two avian strains produced no nonspecific sensitization; in the case of one avian strain (Prague strain), the nonspecific reaction had the same definition as the specific reaction, but was from one-half to three-fourths less in volume; the fourth avian strain also produced hypersensitiveness to the nonspecific tuberculin, but the individual variation in sensitization was quite pronounced. The intracutaneous injection of the nonspecific tuberculin in the groups sensitized by mammalian tubercle bacilli elicited the same variation in hypersensitiveness as was observed in the avian-sensitized animals, but the nonspecific response was even less marked and more inconstant.

CONCLUSIONS

1. A method is described for the differentiation of avian and mammalian tubercle bacilli, which is based on the reactions of guinea pigs, sensitized by avian and mammalian tubercle bacilli, to avian and mammalian tuberculins, respectively.

2. The Calmette *BCG* tubercle bacillus was shown to be of mammalian type.

3. The Friedmann turtle bacillus gave a reaction characteristic of the piscine acid-fast microörganisms.

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TABLE 1

Comparative systemic reactions to avian and mammalian tuberculins in guinea pigs sensitized by pure strains of avian, bovine and human tubercle bacilli, and Calmette BCG tubercle bacillus

Each guinea pig received an intraperitoneal injection of 2 cc. tuberculin per 500 gm. weight.

SENSITIZATION			KIND OF TUBERCULIN	NUMBER TESTED	DIED		SURVIVED		
Type	Strain	*			Within 24 hours	After 24 hours	Strong reaction	Weak reaction	No reaction
Avian	Biochemic Division	35 days	Avian	5	1	3	0	1	—
			Mammalian	5	0	1	0	0	4
Avian	Pathological Division	36 days	Avian	5	3	2	—	—	—
			Mammalian	5	1	0	1	3	—
Avian	Prague	42 days	Avian	5	2	1	0	2	—
			Mammalian	5	1	1	0	1	2
Avian	Experiment Station	32 days	Avian	5	1	2	1	1	—
			Mammalian	5	0	1	1	2	1
Bovine	No. 1,094	29 days	Avian	5	0	0	0	0	5
			Mammalian	5	5	—	—	—	—
Bovine	No. 854	29 days	Avian	5	0	0	0	5	—
			Mammalina	5	3	2	—	—	—
Bovine	No. 642	29 days	Avian	5	0	0	0	0	5
			Mammalian	5	1	2	2	—	—
Human	Biochemic Division	29 days	Avian	5	0	0	5	—	—
			Mammalian	5	5	—	—	—	—
Calmette *BCG*		37 days	Avian	5	0	0	0	0	5
			Mammalian	5	2	1	2	—	—

* Period elapsed between inoculation with tubercle bacilli and testing with tuberculin.

TABLE 2

Intracutaneous test of BCG sensitization

Each guinea pig received an intraperitoneal injection of 5 mgm. of *BCG* tubercle bacilli, 38 days prior to skin test. Test made by injecting 0.1 cc. avian tuberculin intracutaneously on one side of abdomen and 0.1 cc. mammalian tuberculin intracutaneously on the opposite side.

GUINEA PIG	TUBERCULIN	DESCRIPTION OF REACTION	
		24th hour	48th hour
90,713	Avian	No reaction	No reaction
	Mammalian	Plateau swelling, 16 mm. in diameter, inflamed, with pale central area	15 mm. diameter reaction, raised, inflamed, with central necrotic area
90,714	Avian	No reaction	No reaction
	Mammalian	Inflamed swelling, 22 mm. diameter, with pale centre	Raised, inflamed swelling, 21 mm. in diameter, with 5 mm. central necrotic area
90,715	Avian	No reaction	No reaction
	Mammalian	Raised, inflamed swelling, 20 mm. in diameter, with pale central area	Slightly inflamed swelling, 18 mm. diameter with 5 mm. central area of necrosis
90,716	Avian	No reaction	No reaction
	Mammalian	Reaction, 20 mm. diameter, intensely inflamed, with 7 mm. central pale area	Inflamed reaction, 16 mm. in diameter, with 7 mm. central necrotic area
90,717	Avian	Skin slightly thickened and faint rubor	Skin slightly thickened and faint rubor
	Mammalian	Raised, inflamed reaction, 20 mm. diameter, with 6 mm. central area of necrosis	Raised, intensely inflamed reaction, 18 mm. diameter, with 6 mm. central necrotic area

TABLE 3

Intracutaneous test of avian tubercle bacillus sensitization with Biochemic-Division strain

Each guinea pig received an intraäbdominal injection of 5 mgm. of avian tubercle bacilli, 31 days prior to cutaneous test. Test made by injecting 0.1 cc. avian tuberculin into skin on one side of abdomen and 0.1 cc. mammalian tuberculin on opposite side.

GUINEA PIG	TUBERCULIN	DESCRIPTION OF REACTIONS AT 48TH HOUR
90,085	Avian	Raised, inflamed swelling, 24 mm. in diameter, with small central area of necrosis.
	Mammalian	Practically no reaction; skin had a pallid hue, but no evidence of inflammation
90,086	Avian	Raised, inflamed swelling, 25 mm. in diameter, with 1 cm. pale centre
	Mammalian	Very slight reaction; skin slightly thickened with trace of inflammation
90,087	Avian	Raised, inflamed swelling, 15 mm. diameter, with central area of necrosis
	Mammalian	Skin slightly thickened at site of injection, with trace of inflammation
90,088	Avian	Raised, slightly mounded reaction, 15 mm. in diameter, slightly inflamed, with small central area of necrosis
	Mammalian	Skin slightly thickened but pale

TABLE 4

Intracutaneous test of avian tubercle bacillus sensitization with Pathological-Division strain

Each guinea pig received an intraäbdominal injection of 5 mgm. avian tubercle bacilli, 38 days prior to cutaneous test. Test made by injecting 0.1 cc. avian tuberculin into skin on one side of abdomen and 0.1 cc. mammalian tuberculin on opposite side

GUINEA PIG	TUBERCULIN	DESCRIPTION OF REACTIONS AT 48TH HOUR
90,544	Avian	Plateau swelling, 20 mm. in diameter, highly inflamed, with pinkish margin, and 1 cm. pale central area
	Mammalian	Skin thickened at site of injection and "palish", no inflammation or necrosis
90,545	Avian	Raised reaction, 25 mm. in diameter, highly inflamed, with necrotic centre turning brown
	Mammalian	Slight reaction, 1 cm. in diameter; skin thickened and slightly inflamed
90,546	Avian	Plateau swelling, 25 mm. in diameter, inflamed, with 1 cm. central area of necrosis
	Mammalian	Area 6 mm. in diameter, slightly congested and skin thickened
90,547	Avian	Reaction 20 mm. in diameter, of greenish hue, with congested border, and small central area of necrosis
	Mammalian	Skin thickened and blanched over an area 8 mm. in diameter
90,548	Avian	Intensely inflamed swelling, 30 mm. in diameter, raised, with heavy scab 1 cm. in diameter forming
	Mammalian	Area 15 mm. in diameter, skin thickened and slightly congested

TABLE 5

Intracutaneous test of avian tubercle bacillus sensitization with Prague strain

Each guinea pig received an intraäbdominal injection of 5 mgm. avian tubercle bacilli, 38 days prior to cutaneous test. Test made by injecting 0.1 cc. avian tuberculin into skin on one side of abdomen and 0.1 cc. mammalian tuberculin on opposite side.

GUINEA PIG	TUBERCULIN	DESCRIPTION OF REACTIONS AT 48TH HOUR
90,905	Avian	Raised, slightly inflamed reaction, 16 mm. in diameter, with central area of necrosis
	Mammalian	7 mm., raised, inflamed reaction, with small central area of necrosis
90,908	Avian	Plateau swelling, 20 mm. in diameter, inflamed, with central pale area, 1 cm. in diameter
	Mammalian	7 mm. raised swelling, inflamed, with small central area of necrosis
90,913	Avian	8 mm. reaction, raised, inflamed, with small central area of necrosis
	Mammalian	Skin slightly thickened, with trace of inflammation
90,918	Avian	Plateau swelling, 25 mm. in diameter, highly inflamed, with small central area of necrosis
	Mammalian	Area 6 mm. in diameter, raised, inflamed, with well-defined central area of necrosis

TABLE 6

Intracutaneous test of avian tubercle bacillus sensititization with Experiment-Station strain

Each guinea pig received an intraäbdominal injection of 5 mgm. avian tubercle bacilli, 32 days prior to cutaneous test. Test made by injecting 0.1 cc. avian tuberculin into skin on one side of abdomen and 0.1 cc. mammalian tuberculin on opposite side.

GUINEA PIG	TUBERCULIN	DESCRIPTION OF REACTIONS AT 48TH HOUR
91,692	Avian	Raised, inflamed reaction, 14 mm. in diameter, with 4 mm. central area of necrosis
	Mammalian	Skin thickened over an area 7 mm. in diameter, and pale
91,693	Avian	Mound swelling, 11 mm. in diameter, intensely inflamed, with pale central area
	Mammalian	8 mm. area, slightly raised, and slightly inflamed, with small "palish" central area
91,694	Avian	Inflamed swelling, 1 cm. in diameter, with small central area of necrosis
	Mammalian	Skin slightly thickened with trace of inflammation
91,695	Avian	Mound swelling, 1 cm. in diameter, slightly inflamed, with small central area of necrosis
	Mammalian	5 mm. area, skin thickened with trace of inflammation
91,696	Avian	Intense reaction, 35 mm. in diameter, raised, highly inflamed, with central area 18 mm. in diameter becoming necrosed
	Mammalian	20 mm. area, raised, inflamed, with 4 mm. central area of necrosis

TABLE 7

Intracutaneous test of bovine tubercle bacillus sensitization with strain 1,094

Each guinea pig received an injection of 0.01 mgm. bovine tubercle bacilli, subcutaneously, right thigh, 33 days prior to intracutaneous test. Test made by injecting 0.1 cc. avian tuberculin into skin on one side of abdomen and 0.1 cc. mammalian tuberculin on opposite side.

GUINEA PIG	TUBERCULIN	DESCRIPTION OF REACTIONS AT 48TH HOUR
91,792	Avian	No reaction
	Mammalian	Area 16 mm. in diameter, skin thickened and slightly inflamed, with 3 mm. central area of necrosis
91,793	Avian	There was a slight thickening of skin and slight inflammation at the 24th hour, which had practically resolved at the 48th hour
	Mammalian	Raised, intensely inflamed swelling, 20 mm. in diameter, with a central, slightly necrotic area 10 mm. in diameter
91,794	Avian	Area 10 mm. in diameter, mounded and inflamed, with a 5 mm. central area of necrosis
	Mammalian	Raised, intensely inflamed swelling, 30 mm. in diameter, with a necrotic centre 15 mm. in diameter
91,799	Avian	Area 8 mm. in diameter, slightly inflamed and mounded, no necrosis
	Mammalian	Plateau swelling, 20 mm. in diameter, slightly inflamed, with 7 mm. central area of necrosis
91,900	Avian	8 mm. mound, slightly inflamed, with 4 mm. central necrotic area
	Mammalian	22 mm. area intensely inflamed and raised, with 14 mm. central area of necrosis

TABLE 8

Intracutaneous test of bovine tubercle bacillus sensitization with strain 854

Each guinea pig received an injection subcutaneously, right thigh, of 0.5 cc. emulsion of lymph-node tissue of tuberculous guinea pig, 29 days prior to cutaneous test. Test made by injecting 0.1 cc. avian tuberculin into skin on one side of abdomen and 0.1 cc. mammalian tuberculin on opposite side.

GUINEA PIG	TUBERCULIN	DESCRIPTION OF REACTIONS AT 48TH HOUR
91,055	Avian	Skin slightly thickened, no congestion or necrosis
	Mammalian	Enormous reaction, 30 mm. in diameter, raised, central area 1 cm. in diameter, over which a brown scab is forming, surrounded by a "palish" zone with a congested border
91,066	Avian	Area of skin 3 mm. in diameter, slightly mounded and indurated
	Mammalian	Plateau swelling, 16 mm. in diameter, slightly congested, with pale centre
91,073	Avian	Practically no change in skin
	Mammalian	Raised, inflamed swelling, 18 mm. in diameter, with small central area of necrosis
91,074	Avian	Skin thickened and slightly raised at site of injection, no congestion or necrosis
	Mammalian	Plateau swelling about 20 mm. in diameter, raised 4 mm. above surrounding tissue, very inflamed, with 1 cm. central area of necrosis
91,075	Avian	Practically no change in skin
	Mammalian	Raised, inflamed swelling, 24 mm. in diameter, with central area of necrosis

TABLE 9

Intracutaneous test of bovine tubercle bacillus sensitization, with strain 642

Each guinea pig received an injection of 0.01 mgm. bovine tubercle bacilli, subcutaneously, right thigh, 40 days prior to cutaneous test. Test made by injecting 0.1 cc. avian tuberculin into skin on one side of abdomen and 0.1 cc. mammalian tuberculin on opposite side.

GUINEA PIG	TUBERCULIN	DESCRIPTION OF REACTIONS AT 48TH HOUR
91,912	Avian	No reaction
	Mammalian	Raised, inflamed swelling, 20 mm. in diameter, with small necrotic centre, slightly resolved from preceding day
91,909	Avian	Skin slightly mounded over an area 9 mm. in diameter, with brownish hue
	Mammalian	Raised, inflamed swelling, 24 mm. in diameter, with central brownish scab 1 cm. in diameter, whole reaction slightly resolved from preceding day
91,910	Avian	Skin slightly mounded and thickened over an area 8 mm. in diameter, no inflammation or necrosis
	Mammalian	Raised, slightly inflamed swelling, 18 mm. in diameter, with central area of necrosis 7 mm. in diameter
91,911	Avian	Skin slightly thickened, no inflammation
	Mammalian	Raised, inflamed swelling, 30 mm. in diameter, with a sharply circumscribed central area of necrosis 14 mm. in diameter, slightly resolved from preceding day

TABLE 10

Intracutaneous test of human tubercle bacillus sensitization with Biochemic-Division strain

Each guinea pig received an intraperitoneal injection of approximately 0.25 mgm. culture of human strain of tubercle bacilli, moist weight, 32 days prior to cutaneous test. Test made by injecting 0.1 cc. avian tuberculin into skin on one side of abdomen and 0.1 cc. mammalian tuberculin on opposite side.

GUINEA PIG	TUBERCULIN	DESCRIPTION OF REACTIONS AT 48TH HOUR
91,750	Avian	Skin blanched and slightly thickened over an area 15 mm. in diameter
	Mammalian	Plateau swelling, 25 mm. in diameter, central necrotic area surrounded by a brownish colored zone with peripheral congested border
91,751	Avian	Slightly inflamed mound, 1 cm. in diameter, no necrosis
	Mammalian	Intensely inflamed swelling, 40 mm. in diameter, with a 20 mm. central area of necrosis
91,952	Avian	Brownish mound, 9 mm. in diameter, no necrosis
	Mammalian	Skin thickened and slightly inflamed over an area 30 mm. in diameter, with central area of necrosis 6 mm. in diameter
91,760	Avian	Skin slightly thickened and slightly inflamed over an area 8 mm. in diameter, no necrosis
	Mammalian	Raised, inflamed swelling, 20 mm. in diameter, with 5 mm. central necrotic area
91,761	Avian	Skin thickened and slightly inflamed over an area 8 mm. in diameter, no necrosis
	Mammalian	Raised, slightly inflamed reaction, 30 mm. in diameter, with 6 mm. central necrotic area

STUDIES IN TUBERCULOSIS

VIII. THE IDENTIFICATION OF A SKIN-REACTING SUBSTANCE IN TUBERCULOUS SERA[1]

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with the assistance of

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In the experiments to be reported a biological method has been devised for identifying a specific skin-reacting substance in the blood-serum of tuberculous patients and animals. In principle, the procedure depends upon a living "indicator," which can reasonably be assumed to measure related or identical elements in the serum to be tested. The problem was concerned with the nature of reacting substances in tuberculous serum, and more specifically with the unity or multiplicity of such substances.

The point of departure was an earlier observation reported elsewhere (1), that sensitization in normal animals could be accomplished with fractions of tuberculins prepared from nonprotein substrates. Such a method appeared to furnish a fundamental requirement, subject at once to rigid experimental control, while assuring immunobiological reactions free from the shortcomings of *in vitro* methods.

EXPERIMENTAL

Duplicate series of healthy white guinea pigs, weighing 450 to 500 gm., were used in each set of experiments grouped so as to include

(1) Normal guinea pigs previously injected with tuberculin fractions,
(2) Normal untreated guinea pigs, and
(3) Tuberculous guinea pigs with early, moderately advanced, and far-advanced infections.

[1] A preliminary report of this work was given before the Society for Experimental Biology and Medicine at a meeting of the American Association for the Advancement of Science, Mills College, California, June 17, 1926.

[2] Department of Medicine and the George Williams Hooper Foundation for Medical Research, University of California, San Francisco.

TABLE 1

EXPERIMENTAL SERIES	HUMAN SERUM				GUINEA-PIG SERUM		NORMAL HUMAN SERUM	ADENOPATHY FOLLOWING TEST
	Arrested early tuberculosis afebrile, nontoxic	Far advanced tuberculosis with profound toxemia and cavitation	Early tuberculosis	Far advanced tuberculosis	Early tuberculosis	Moribund		
			Serum heated 60–65° for 45 minutes in water bath					
Guinea pigs sensitized with tuberculin fractions:								
Alcohol-insoluble Fraction A	0.5 x 0.5 cm. with induration and reddening and central infiltration	0.5 x 0.5 cm. with induration, reddening and central infiltration	0.3 x 0.3 cm. with slight induration and slight reddening	Negative	0.5 x 0.5 cm. with reddening, induration and central infiltration zone	0.2 x 0.2 cm. with reddening and induration	Negative	Marked
Alcohol-insoluble Fraction B	0.5 x 0.5 cm. with induration and reddening	1.0 x 0.5 cm. with induration and reddening			0.5 x 0.5 cm. with induration, infiltration and reddening	0.3 x 0.3 cm. with slight induration and reddening. Negative after 48 hours	Negative	Marked
Ether-insoluble Fraction A	0.5 x 0.5 cm. with induration, reddening and central infiltration	0.5 x 0.5 cm. with marked induration, reddening and central infiltration	0.3 x 0.3 cm. with slight induration, no reddening	0.3 x 0.3 cm. with negligible induration, no reddening. Negative after 48 hours	1.0 x 0.75 cm. with induration, reddening, erythema zone and central infiltration	0.5 x 0.3 cm. with induration and reddening	Negative	Marked
Ether-insoluble Fraction B	0.2 x 0.2 cm. with reddening and slight induration. Negative after 72 hours	0.4 x 0.3 cm. with induration, reddening and central infiltration			0.5 x 0.5 cm. with induration, reddening and zone of infiltration	0.2 x 0.2 cm. with slight reddening	Negative	Marked
Ether-soluble Fraction A	0.4 x 0.3 cm. with induration, reddening and erythematous zone	0.5 x 0.5 cm. with marked induration, reddening, infiltration and erythema			0.5 x 0.5 cm. with induration, infiltration and reddening	0.3 x 0.3 cm. with slight induration and reddening. Negative after 48 hours	Negative	Marked
Ether-soluble Fraction B	0.2 x 0.2 cm. with slight induration and slight reddening. Negative after 72 hours	0.3 x 0.3 cm. with marked induration, reddening and infiltration			0.5 x 0.5 cm. with induration, reddening and central zone of infiltration	0.3 x 0.2 cm. with induration and reddening. Negative after 72 hours	Negative	Marked

Unfractionated Tuberculin A	0.4 x 0.3 cm. with induration, reddening and slight erythema	1.0 x 1.0 cm. with marked induration, reddening, infiltration and central zone	After 24 hours slight reddening and no induration. After 48 hours 0.3 x 0.3 cm., with slight induration	Negative	0.75 x 0.5 cm. with induration, reddening and infiltration	Negative	Negative	Marked
Unfractionated Tuberculin B	0.3 x 0.3 cm. with induration, reddening and slight erythema	0.75 x 0.5 cm. with marked induration, reddening and infiltration			1.0 x 0.75 cm. with induration, reddening and infiltration	Negative	Negative	Marked
Tuberculous guinea pigs:								
Early tuberculosis	Negative	After 96 hours 0.2 x 0.2 cm. with slight induration and slight reddening					Negative	Previously present and increased
Moderately advanced tuberculosis	0.4 x 0.3 cm. with reddening and induration	0.5 x 0.4 cm. with marked induration, reddening and infiltration	Negative	Negative			Negative	Marked
Far-advanced tuberculosis	Negative	Negative after 48 hours. After 96 hrs., 0.2 x 0.5 cm. with reddening and induration	Negative	Negative	Negative	Negative	Negative	Marked
Normal guinea pigs:	0.5 x 0.5 cm. with induration and reddening	0.5 x 0.5 cm. with induration and reddening	Negative	Negative	0.3 x 0.2 cm. with no induration or reddening	Negative	Negative	None

Normal guinea pigs did not exhibit the residual pigmentation and scarring which characterized the positive tests in the other series of animals.
Readings represent maximum reactions, which occurred usually 24 to 48 hours after intracutaneous tests were made.

Animals in groups (1) and (2) were tested separately with the following materials:

(a) Human sera from early and far-advanced tuberculosis.
(b) Same sera at 60–65°C. on water-bath for 45 minutes.
(c) Normal human serum.
(d) Guinea-pig serum from early and moribund stages of tuberculosis.

Animals in group (3) did not receive all of the test materials, in order to avoid undue repetition.

Technique: Tuberculin fractions were prepared fom nonprotein synthetic media[3] according to the method described in previous publications (2), and represented alcohol-insoluble, ether-insoluble and ether-soluble fractions, and unfractionated tuberculins. The material derived from the glycerine-free substrate is designated in table 1 as the (A) fraction and the glycerinated substrate as the (B) fraction.

Guinea pigs in series 1 were injected subcutaneously with increasing doses of one of the fractional tuberculins over a period of seven weeks. An initial dose of 0.1 cc. and a final dose of 0.7 cc. were given in a total amount of 2.2 cc. Ten to fourteen days after the last injection, intracutaneous tests were applied. The sera, obtained with scrupulous care from patients and animals, were tested for sterility, and subjected to no other treatment except as noted in the experiments with heated serum. All injections were made within two hours after the withdrawal of sera. The abdominal region of the guinea pigs was shaved and thoroughly cleansed prior to injection of 0.02 cc. of the test material. Luer syringes with 27-gauge needles were used. Reactions were recorded after 24, 48 and 72 hours, and observations made until the sites of injection appeared normal. Concomitant changes such as adenopathies were sought and noted.

SUMMARY OF RESULTS

Positive reactions appeared within 24 to 48 hours, and were uniformly characterized by marked induration and infiltration of the site of injection, with varying degrees of erythema surrounding the area, which measured 0.5 to 1.0 cm. in diameter. In most instances there were additional changes, such as central edema followed by necrosis and pitting.

[3] Tuberculins were prepared and donated by Eli Lilly and Company, Indianapolis, through the courtesy of the Biological Department (Dr. W. A. Jamieson, Director), to whom grateful acknowledgment is made.

In general, positive tests showed definite tissue changes for 4 to 10 days after the intracutaneous injections, with residual scarring and localized pigmentation.

The results of this investigation, summarized in table 1, show that groups of normal, sensitized, and tuberculous guinea pigs react differently toward intracutaneous injections of minute amounts of blood-serum from tuberculous patients or animals. The specific skin reactions elicited by a test appear to depend upon the stage of tuberculous infection to which the serum corresponds. Observed differences are referable to an early or a far-advanced tuberculous process, and, if this has been arrested, to the presence or absence of toxemia. This relationship of serum and its source is influenced, moreover, by the stage of tuberculosis in the test-animal. Furthermore, heating tuberculous serum at a temperature of 60–65°C. reduces a skin reaction markedly, or extinguishes it completely when all other conditions are kept constant. Normal guinea pigs, for example, react positively toward tuberculous serum, but do not give a skin reaction with the same serum heated. A similar effect is noted in the group of normal animals sensitized previously by repeated injections of tuberculin fractions, and also in the groups of tuberculous animals. Sera from tuberculous guinea pigs in a moribund state give a delayed and transitory skin reaction, or a negative one in animals ordinarily responding in varying degree to sera from early or advanced tuberculosis. Finally, normal human or guinea-pig serum fails to elicit any reaction whatever in the different groups of animals. As evidence of a more general tissue response in reacting guinea pigs, there is a pronounced inguinal adenopathy.

DISCUSSIONS OF RESULTS

Deductions from the foregoing observations point to the *identification of a heat-labile element in blood serum from tuberculous patients. It exists independently of tuberculin-like substances and is different from these. In all probability this substance is a toxin liberated by the tubercle bacillus, and is present in largest amounts in far-advanced infections with a clinical picture of toxemia.* A study of the behavior of this substance under experimental conditions described in the present report favors such a viewpoint.

Reference to table 2 will aid the interpretation of results listed in table 1. All of these can be explained on the basis of addition or subtraction of one or more interacting substances in tuberculous sera and in

the tissues of the experimental animal. For example, a group of normal, tuberculin-sensitized guinea pigs reacts more violently to intracutaneous injections of serum from advanced toxemic tuberculosis than to serum from an early, nontoxic, arrested infection. While reactions in the first instance are more persistent and residual signs more pronounced, in the latter these are less marked and more transitory. From table 2 it may be seen that this group of animals is strongly endowed with tuberculin-reacting elements and with antibodies for products of tubercle bacilli.

TABLE 2

Schema of reaction phenomena in tuberculosis

INTERACTING SUBSTANCES	GUINEA PIG					TUBERCULOUS SERUM				NORMAL
						Early, arrested, afebrile, nontoxic		Far advanced with profound toxemia		
	Normal	Early tuberculosis (slight toxemia)	Moderately advanced tuberculosis	Far-advanced tuberculosis	Normal tuberculin sensitized		Heated 60–65° for 45 minutes		Heated 60–65° for 45 minutes	
Tuberculin reacting element (heat-resistant)	0	++	±	0	+++	++	++	0	0	0
Toxin (heat-sensitive)	0	±	+	++	0	0 or ± (?)	0	++	0	0
Antibody for tubercle products (probably somewhat heat-sensitive)	±	+	±	0 or ± (?)	++	+	± or + (?)	0 or ± (?)	0	±

The signs 0, ±, +, ++, +++, represent relative quantities of designated substances in tissues or serum, in accordance with immunological and clinical facts.

Injection of the serum causes an augmented reaction by introducing appreciable amounts of toxin. Similarly, in the same group of guinea pigs the test results negatively when the serum is heated at a temperature of 60–65°C. for 45 minutes before injection. Reference to the table shows that the toxin is not introduced under these conditions. In the untreated normal guinea pig, a positive reaction is likewise obtained with unheated serum, owing to the interaction of the toxin and normal antibodies. In the group of tuberculous animals, skin reactions are conditioned by the relative amounts of toxin, antibody for tubercle products

and tuberculin-reacting elements present in the tissues at a given time. These factors, obviously, are modified by the stage of tuberculous infection existing in the guinea pig. Thus we have *a means of measuring circulating antibodies in normal and tuberculous persons and a test which may prove to be an index of bodily resistance to tuberculosis.*

It has been shown clinically and the experimental evidence submitted here indicates that tuberculin-reacting elements are absent in cases of far-advanced tuberculosis. In such patients tuberculin tests are uniformly negative. The opposite is true in early tuberculosis, particularly when little or no toxemia is present. The tuberculin element, moreover, is heat-resistant to an extraordinary degree, as has been demonstrated by other investigators and also in earlier studies with acetanhydride derivatives (3).

Of interest in connection with the foregoing observations are the results reported by Lenz (4) and Henrichsen and Sweany (5) on an autoserum test for tuberculosis. The interpretation given by these investigators, particularly the latter group, does not seem consistent with the observed facts. Furthermore, they assume certain things to be true, and thereby vitiate such positive evidence as their experiments might have afforded. To quote from the first paper by Henrichsen and Sweany, it was noted that a strong reaction seemed to indicate a poor prognosis, showing that the antigenic substance in the serum was present in a higher concentration, or that these cases had a greater degree of skin hypersensitiveness due to the disease. In a subsequent report it was stated by the authors that positive reactions in nontuberculous conditions were attributable to antigens other than those of tuberculosis in the body, and to skin hypersensitiveness which they assumed to be present in all chronic toxemias. In their animal experiments, tuberculous as well as normal guinea pigs gave similar reactions, and on these grounds the tests were further considered as having no value. These explanations do not appear to be adequate or convincing, and, in the absence of a suitable experimental method, an interpretation of such results must, of necessity, be ambiguous.

The evidence presented in the present study suggests a reasonable explanation for a controlled series of observations, and the deductions seem to fit immunological facts. From such a standpoint, the mechanism of the reactions is perhaps analogous to a type of Arthus phenomenon. It is possible to obtain skin reactions by intracutaneous injections of antibody into animals previously treated with a corresponding or related

antigen. Similarly, a tuberculous animal, depending upon the stage of infection, will give a response in terms of the same fundamental principle. These considerations find experimental support in some of the recent studies by Opie (6), in which are discussed the meeting of antigen and antibody within susceptible tissues.

CONCLUSIONS

1. A heat-sensitive skin-reacting substance of the nature of a toxin has been identified in the blood-serum of tuberculous patients and guinea pigs. It is not found in normal human or guinea-pig serum. The substance does not behave like tuberculin or its related elements, which are heat-resistant, and exists independently of these. It is present in largest amounts in far-advanced tuberculous infections with profound toxemia, and is apparently destroyed by heating at 60–65°C. for 20 to 45 minutes. In normal animals this unheated substance gives a positive skin test, owing to its interaction with normal antibodies for tubercle products.

2. The method devised for identifying this specific skin-reacting substance depends, in principle, upon a living "indicator," the guinea pig, which measures related or identical elements in the serum to be tested. The procedure was made possible by a previous demonstration that normal animals could be sensitized with fractional tuberculins prepared from nonprotein substrates.

3. Skin reactions, obtained according to the technique described in these experiments, are referable to an addition or subtraction of one or more of the interacting substances present in tuberculous serum and in the tissues of the experimental animal.

4. Evidence is adduced to show that the heat-labile substance, probably a toxin, in tuberculous sera, can be used as a measure of the circulating antibodies in normal and tuberculous persons. A test of this type may serve as an index of the bodily resistance to tuberculous infection in both groups.

Certain theories and hypotheses regarding tuberculin and skin sensitiveness in tuberculous and normal persons and animals find an interpretation based on controllable experimental evidence. An explanation is offered for negative tests in far-advanced tuberculosis, and, furthermore, positive reactions with tuberculous sera in apparently normal persons are to be attributed to a toxin. Accordingly, the results with the autoserum test of Lenz (4) and modified autoserum (5) and Wildbolz reactions (7) take on a somewhat different aspect.

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THE ANATOMICAL STRUCTURE OF TUBERCLE FROM HISTOGENESIS TO CAVITY[1]

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An invitation to address *The International Union Against Tuberculosis* is a cherished honor, long and appreciatively to be remembered; yet, when faced by the subject selected by your Committee, the speaker's first feeling cannot help being one of uncertainty, and perhaps bewilderment. *The Anatomical Structure of Tubercle from Histogenesis to Cavity* has inspired a corpus of exposition which alone outmeasures that five-foot shelf confidently promised to encompass the entire mental equipment of the American gentleman. Surely, one more morphological account, documented and sequential, could be but a shallow and inferior repetition of what has been often and well said before.

As regards its discernible elements of *form*, the structure of tubercle would seem to be peculiarly well understood; Baillie, Laennec, Virchow, and almost every great pathologist since Virchow have winnowed out and repieced the record here, and the record stands unusually full and complete. Quite different, however, appears the structure of tubercle in its functional relations,—those aspects of structure which will be always of greatest interest and importance for us who would understand the *disease* tuberculosis. As John Hunter might say, we have learned our alphabet, the several forms that enter into the structure of tubercle, but what language does it speak,—what do these forms tell us about what the structure of tubercle does,—what purposes have been subserved in the development of characteristic forms, and what functions do these forms fulfil after they have been developed?

Or, more concretely, why is tubercle the bodily response to tubercle bacilli? How does tubercle behave toward tubercle bacilli? How, again, does it behave toward the body?

[1] An address on the research subject, *The Anatomical Structure of Tubercle from Histogenesis to Cavity*, delivered at the *Fifth Conference of the International Union Against Tuberculosis*, Washington, D. C., October 1, 1926.

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It is to a consideration of such questions, in terms of structure, that perhaps the larger part of the remarks which follow will be addressed. We may not look for disclosures as definite and objective as the eye and the microscope will reveal for the morphology of structure. Probability must be our guide; nevertheless, a probability, it is hoped, that will not stray too far from a basis of authenticated fact.

By "Tubercle" is Understood All Anatomical Responses to Tubercle Bacilli

What, first, shall we understand by *tubercle?* Strictly speaking, the term signifies a rather typical nodular formation resulting from a variety of conditions; and, more specifically, the well-defined and characteristic *nodular* tissue product of the activities of tubercle bacilli. Yet, if we limit our vision to this type of structure we shall overlook some of the most common and important anatomical formations of tuberculosis. There is much to tuberculosis which, structurally, has little or nothing of the nodular or *tuberculoid* about it. There are, for instance, diffuse inflammation and suppuration, and effusions of varied kind. All are evoked by tubercle bacilli. Every one must be brought into any consideration of the anatomical structure of tuberculosis,—if for no other reason than that we may comprehend the real *inwardness* of the more special *tubercle* itself. While, ordinarily, we thoroughly dislike going beyond the morphological connotations of *tubercle*, we shall, for our present purpose, use the term as broadly synonymous with *tuberculosis*, anatomically considered, to denote every kind of formation instigated in animal tissues by tubercle bacilli.

Tubercle May Be Conceived as of Two Types—Nodular and Non-Nodular

The almost infinite variety of anatomical guise of tuberculosis need hardly be dilated upon before this audience of experts. Out of what, to the uninitiated, seems a hopelessly confused jumble of effects, there gradually dawns the suggestion that, however diverse they may be otherwise, the morbid structures separate out into one or the other of two fundamental groups: either they are nodular or they are non-nodular. If they are nodular, they are more or less roughly globular, circumscribed and discrete; if non-nodular, they are likely to be much more irregular in outline, and diffuse, and with few or no features of investment. Having noticed this distinguishing feature, the novice has grasped the first

principle of the modern pathology of tuberculosis,—the basis upon which Laennec erected his prescient edifice, the doctrine of the unity of phthisis, with materials derived through the use of his unaided vision alone.

Nodular Tubercle Represents the Native Anatomical Response of the Tissues to Tubercle Bacilli

Now, all nodular tubercle, of whatever external appearance and whatever extent, is the resultant, and almost invariably the multiple, of smaller and more elementary nodular tubercles. Its primitive components began as minute nodular tubercles; as microscopic spheroids, called into being by the activities of tubercle bacilli. Indeed, it is as nodular tubercle, and nodular tubercle only, that anatomical tuberculosis can *originate* in the animal that is susceptible to tubercle bacilli. It therefore follows, of necessity, that nodular tubercle represents the *native* capacity of the susceptible animal's tissues to react to the bacilli. This most important fundamental generalization is based on observations unfailingly yielded by controlled experimentation, as will be related immediately. In the circumstances, for reasons that will appear, it could not be formulated from the data of human clinical and pathological examination.

Non-Nodular Tubercle Represents a Newly Acquired Allergic Anatomical Response to Tubercle Bacilli

As is well known, the establishment of tubercle endows the latter's possessor with the capacity to react to tubercle bacilli in a new way, one that eventuates in non-nodular anatomical formations. We recognize this newly acquired attribute as the *allergic state*, and the product or resultant of contact of tubercle bacilli with tissues of an animal thus equipped, as the *allergic reaction*. The allergic state becomes detectable soon after an animal becomes tuberculous (infected) *for the first time;* and from then on ever responds to the activities of tubercle bacilli as long as these remain within the body. It happens, therefore, that every tuberculous animal is capable of meeting tubercle bacilli in at least two ways: namely, in the original manner of its native constitution and in the manner of allergy.

Since the allergic state can come into play within two weeks, more or less, after the first focalization of tubercle bacilli within the body, all later tissue effects must be regarded as having been variably influenced and moulded by allergy. Accordingly, the character of an animal's

native anatomical response to tubercle bacilli can be unimpeachably ascertained only in that short period that intervenes between the *first* contact of bacilli with the tissues and the awakening of allergic action. And it now becomes obvious why the disclosure of how "virgin" tissue soil reacts to tubercle bacilli requires recourse to experimentation.

Morphological Description of the Origin and Early Evolution of Primary Nodular Tubercle

Nothing can be more regular and uniform than the early series of events that follow a *first* tuberculous infection at the site of infection,—a series which we may think of as representing the first or pre-allergic anatomical phase of tuberculosis. This constancy of more immediate effects is all the more noteworthy and significant in that it is not *essentially* modified by such variables, otherwise decisive, as the numbers and type of mammalian tubercle bacilli concerned. The experimental inoculation should be made in a superficial placewhich is accessible to continuous observation,—in the cornea or within the skin (intracutaneously).

Following the ephemeral traumatic remains of a well-performed inoculation there pass a few uneventful days: nothing whatever is visible at the spot, let us say in the skin, where the bacilli were introduced. Then, arising out of a noninflamed background, a pale and rounded nodule comes into view. It has taken perhaps a week to become visible or palpable. Still pale or, maybe, a little livid, firm also and indurated, and bordered by a peculiarly little altered setting of unaffected skin from which it is sharply delimited, it leisurely enlarges in the manner of an expanding spheroid.

Now, as we are well along in the third week after inoculation, we are likely to notice the nodule and its surrounding border of skin undergoing changes. The nearly rounded nodule gradually assumes a more irregular outline as the latter extends eccentrically out into its setting of skin; and at its centre the nodule displays a point of deepening opacity and a transition to a whiter or yellowish-white color, Here, too, the rubbery induration of the nodule is going over into a doughy consistence. At the same time, the zone of skin immediately embracing the nodule is taking on a pinker hue, which is also appearing in the more peripheral portion of the nodule itself; and in the encircling pink skin may be one or a very few minute pale and indurated nodules, lying juxtaposed to the larger primary nodule or apparently incorporated in part with its rim. We know from experience that when this second group of changes becomes

visible the animal's pre-allergic phase of tuberculosis has been completed, and that all anatomical features of its *strictly* and *exclusively* native reaction to tubercle bacilli already belong to the past.

Close attention to the evolution of this nodule, as far as we have followed it, will have taught us the following:

First: It represents the invariable early anatomical response of all tissues of a susceptible animal brought in contact with tubercle bacilli for the first time. More than this,—it typifies the *only* early anatomical response which such tissues will make. Nodular tubercle is, therefore, the type of structure devised by the susceptible animal, unaffected by allergy, to meet the activities of tubercle bacilli; in other words, let us repeat, it is the structure that originates by virtue of an animal's *native* capacity to respond to tubercle bacilli. But, it should also be remembered that, when an animal acquires new capabilities of anatomical reaction, it does not lose its native power to form nodular tubercle. This remains, and is, as we shall see, perhaps enhanced.

Second: Nodular tubercle develops in a slow and indolent manner.

Third: It is sharply delimited from the tissue in which it is set.

Fourth: It comes into being without the cardinal signs of acute inflammation. It arises without redness (*rubor*) or heat (*calor*). Pain (*dolor*) is probably lacking intrinsically, and will occur only by reason of location. Swelling (*tumor*), it is true, takes place; but this is a swelling that is more comparable to that of neoplasm rather than of inflammation.

Fifth: After first nodular tubercle is well established, signs of inflammation, as represented by redness, begin to appear. They are noticeable first in the zone of nontuberculous tissue immediately surrounding the nodular tubercle, and then in the outer portion of the tubercle itself.

Morphological Description of Minute Structure of Early Nodular Tubercle

The minute structure of this primary nodular tubercle of ours is characteristic and well known. It is made up of several elementary tubercles, aggregated with their peripheries apposed, to form themselves the spheroid which we see with the naked eye. Each component elementary tubercle is a microscopic spherical nodule itself, constituted for the most part of cells that are so characteristic that they may be called the *essential* cells of *nodular tubercle*,—the latter's *sine qua non*. Resembling epithelial cells in their early state, and therefore designated *epithelioid* cells, an important thing to know and remember about them is that they are not derived from epithelium and have nothing to do with epithelium.

Each separate collection of epithelioid cells,—that is, each elementary tubercle,—invests or englobes, or has englobed, one or more tubercle

bacilli. These bacilli reside originally at or near the centre of the individual cell spheroids.

A properly stained cross-section of our primary nodular tubercle will therefore disclose circular masses of these cells set side by side. The cells of the individual masses will have a whorled or roughly onion-layered arrangement, that is especially noticeable in the more peripheral whorls, where also the epithelioid cells will be more flattened and elongated than toward the centre of the mass. In the latter location the cells retain more their original shape and contour; that is, they tend to be round or ovoid; and, passing from the centre to the periphery, they gradually make the transition to the more flattened and elongated shapes mentioned. In the outer layers of the mass, fibrils appear. The interlacing of these fibrils, together with the progressive flattening, and even eventual imbrication, of the outer cells, will little by little convert the outer part of each cell-mass into the simulacrum of an investing tissue. Frequently at or toward the centre of an elementary tubercle, an unusually large and multinucleated cell comes to view,—the well-known giant cell of Langhans, a common though in no way invariable or necessary constituent of tubercle. If giant cells are present and tubercle bacilli also, the latter are most likely to be found within the giant cells; but if, as is the more common occurrence in early experimental tuberculosis, there are no giant cells, the bacilli reside, in most instances, near the centre of the tubercle, within epithelioid cells or lying free outside these. Nevertheless, in these early and incompletely evolved tubercles, a few or single bacilli are often to be seen at any zone of the cross-section of the tubercle; and out, indeed, to the very periphery. But the *tendency* for them to be aggregated in the general neighborhood of the centre of the elementary tubercle is no doubt important to an understanding of the function of tubercle, and should be noted.

In these elementary tubercles of ordinary experiment we will nearly always see another type of cell, besides the epithelioid cell, entering into the formation of the primitive cell-mass. This type is manifestly the lymphocyte, which does not, in this location, change its morphological character. It is present in variable numbers, and is distributed throughout the plane of the cross-section, always more numerously at the periphery of the epithelioid masses, and diminishing toward the centre.

Just as each elementary tubercle has, through a closer packing down of cells and a laying down of fibrils, its periphery more or less marked off into an investing envelope, so the general or common periphery of all

the constituent primitive cell-masses is converted into a shell-like tissue, which forms the investment of our visible primary tubercle and delimits the latter from the surrounding normal tissue.

Thus, as far as we have gone, we may regard our nodular tubercle as a composite structure made up of several epithelioid-cell spheroids, each of which englobes or has englobed tubercle bacilli. We have several times called the *epithelioids* the *essential cells* of tubercle. We can prove this signification by inoculating tissues with *very few* tubercle bacilli. In this event we find uniformly that for a few days the epithelioid cell is the single tissue component of microscopic tubercle later, and little by little, lymphocytes enter the structure. If we may speak of such a thing as the "pathognomonic structure" of tubercle, then we should define it as a spheroidal and whorled mass of epithelioid cells, or an aggregation of such masses; the presence of giant cells adds probability to the tuberculous origin of the structure; so does the appearance of lymphocytes properly disposed; the finding of tubercle bacilli clinches the matter. Epithelioid cells, onion-layered, may alone be seen, as tubercle bacilli have disintegrated and disappeared; it is a tubercle. Tubercle bacilli may alone be present; it is not a tubercle. Nor is it one if lymphocytes alone display themselves, or a giant cell alone.

Character of Process That Gives Rise to Nodular Tubercle: Evidence That It Is Fundamentally a Proliferation of Cells in Situ

If we eliminate all disturbing factors that may arise through the inoculation of too large quantities of tubercle bacilli, we may arrive at a true appreciation of the character of the process which gives rise to the aggregations of epithelioid cells which form primary tubercle. In response to the localization of a very few bacilli and during the first few days after localization, we find that not a vestige of tissue disturbance occurs except at and around the immediate point of localization of bacilli. Between this site and any other point we cannot trace the slightest evidence (anatomical) that the bacilli have exerted the least effect on any other cells than those in the immediate neighborhood. Save for the completely isolated aggregation of epithelioid cells, enclosing tubercle bacilli, the microscopic field discloses entirely normal tissue,—of lung or cornea for instance. At the same time, within the epithelioid masses cells in active mitosis are frequently to be observed.

These two phenomena compel the opinion that the *origin* of nodular tubercle, that is, the first aggregation of epithelioid cells, is accomplished

through the *proliferation*, in other words the new growth, of cells at or near (within microscopic distance of) the point of localization of tubercle bacilli, and normally existing there. While, from the very beginning, elements from the blood,—serum, leucocytes, red blood cells, etc.,—may enter into the structure of nodular tubercle, they (and therefore exudation) are not an *essential* part of the formation of primitive tubercle. The extent to which they will appear will depend on such variable factors as "dosage" of localizing bacilli, physical character (integrity) of bacilli, nature of inoculation menstruum, traumatization of tissues, etc. Properly adjusted "dosage" and properly selected tissue (the avascular cornea is ideal) are indispensable for the correct adjudication of the basic process engaged in the formation of tubercle; just as is the further condition that the problem must be settled within the first four or five days after a *primary* inoculation,—before allergy can get under way. Then, with these requirements fulfilled, all signs point to the fact that *tubercle originates as a proliferative process.*

Discussion of Origins of Component Cells of Nodular Tubercle

Where experts cannot agree, the wise novice will be wary. Call the parent cell of the epithelioid cell what you will,—*endothelial cell, histiocyte, clasmatocyte, reticular cell, fibroblast, monocyte, reticulo-endothelial cell*, etc., etc.,—added years of uninterrupted observation of the genesis of primitive tubercles have served only to strengthen the idea of at least one worker that this parent cell, as has been said, exists *in situ* and, *in a thoroughly topographical sense*, may be thought of and designated as a *fixed-tissue cell:* that is, it is not exuded from blood or lymph, or "called," as by *taxis*, from a distance in response to tubercle bacilli. The first purely epithelioid-cell tubercles, which arise in the cornea in response to *minimal* numbers of tubercle bacilli, are just as surely and as characteristically primitive tubercles as are tubercles anywhere else. They are constituted of the same basic and essential cell; yet we know of no anatomical connection that is detectable as bridging the gap between this avascular tissue and vascular structures nearby. Again, except in a very few selected locations, as, for instance, the capillaries of the liver, an *intraluminal* or *intimal* origin of tubercle, set up by bacilli of haematogenic origin, is a rare event. In almost all cases blood-borne bacilli will instigate tubercle in the adventitia, if the tubercle is in relation to the blood-vessels at all. One wonders also why the cells of the lymphatics, perhaps some cell of their endothelium, or of lymphoid tissue, perhaps its

reticulum cell, are so often disregarded in accounts of the genesis of tubercle. For, lymphatics and lymphoid tissue are far and away the great depositories and repositories of tubercle bacilli (as of all foreign particles) within the body; and lymphoid tissue, some one of its constituents, does react and proliferate to foreign particles and to tubercle bacilli; and lymphatic tuberculosis is, in point of incidence, the most frequent tuberculosis that exists.

Accordingly, until cytologists are more in accord, it would appear altogether premature to "take sides" on the origin of the epithelioid cell. Broad considerations, which must enter into any final determination of the question, have been stated above. For our present purpose, and in the absence of compelling testimony to the contrary, it is enough to view the epithelioid cell as derived by proliferation from cells existing *in situ* at the time of focalization of tubercle bacilli. We leave to the future the precise determination of the parent cell and its nature.

Giant cells must be regarded as originating from epithelioid cells. As to their exact genesis, one may have two "guesses;" either that they began as single epithelioid cells that came to enclose bacilli, and by so doing have been harmed to an extent that they cannot complete their division into daughter cells, a limited power of nuclear mitosis remaining the while; or that they have been formed by the fusion of several epithelioid cells, whose individual nuclei survive as their cell membranes disappear.

Without committing oneself, it may be stated from personal experience that there may be observed unexceptionable *morphological* appearances to support either opinion. But an adequate decision must take into account such particulars as the ordinarily central location of the giant cell in the primitive tubercle; the general tendency of the cell to contain bacilli; the frequency with which the cytoplasm of the cell presents the accepted histological appearance of beginning degeneration—often the only constituent of the tubercle to do so; and the circumstance that, in general, a concept of the fusion of active and vigorous cells into a single larger multinucleated cell runs counter to pathological orthodoxy, while the formation of a "monster" or the stimulation to aberrant development through cell-damage has numerous analogues. At the very least the burden of proof is on the advocates of the idea of fusion; moreover, we believe that, while it can be very suggestive, the behavior of cells or tissues in artificial cultivation (*in vitro*) must, in the present state of our knowledge, be applied with great caution and a minimum of dogmatism to analogous relations within the body.

We have already anticipated our treatise a bit when we described above how the gradual transition of *epithelioids* from rounded to flattened cells and their imbrication through being packed down in the more peripheral layers, together with the laying down and interlacing of fibrils, gave rise to the image of a peripheral investing tissue, which might be presumed actually to function as such. As long as Baumgarten's concepts of tuberculogenesis enjoyed their almost unchallenged vogue it was not difficult to rationalize this evolution. Cells of "connective-tissue type," as the parent cells of the *epithelioids* were imagined to be, would naturally be thought to pass over again into connective tissue as the more embryonic rounded *epithelioids* went through their cycle into more fusiform and finally mature types. More recent developments, with their advocacy of even leucocytic types of cells as the ancestors of the *epithelioids*, if confirmed and generally accepted, would, of course, render untenable any opinion that looked to the epithelioid cells for the progenitors of the cells which later entered into the formation of the fibrous capsule of tubercle, and would make necessary the discovery of a new constituent cell of primitive tubercle to account for this peripheral fibrous transformation.

Now, on morphological grounds alone, this transition from central round to peripheral flattened epithelioids has always seemed as plain as microscopic images can be; so clear, indeed, that the morphologist might be justified in thinking that, solely from his point of view, it did not matter from what the epithelioid cell was derived. In its later stages the latter manifestly flattened out and arranged itself in overlapping layers, and even threw out fibrils, notwithstanding the impossibility of its forming fibrous tissue, according to the postulates of the cytologist or embryologist.

How difficult it may be, because of insufficient knowledge and prematurely conceived opinions, to follow consecutively and rationally all the stages in the evolution of as simple a formation as the primitive tubercle, is illustrated in this very connection. There can be no doubt that, as we shall see later, peripheral fibrosis is part of the cycle of every normal tubercle. We have just remarked how obvious appears the transition from epithelioid cells (whatever they may be at bottom is immaterial here) to peripheral fibrosis in early tubercles. Now comes the view, as developed particularly by Cunningham and Sabin and their associates, that the *epithelioids* of tubercle are derived from *monocytes*. But, we are told that monocytes cannot form a tissue; and, if we accept

both opinions, that is, that *epithelioids* come from monocytes and that monocytes cannot form a tissue, we cannot square what appears to be well authenticated by one method of study with what seems to be plainly visible under the microscope.

That monocytes cannot form a tissue is a dictum based on the observation of monocytes in tissue culture. But, recently, when Carrel and Ebeling (*Jour. Exper. Med., 1926, xliii, 461*) grew monocytes in cultures under modified conditions, they found that the *monocytes became transformed into fibroblasts*, whenever mechanical factors packed the monocytes together; in other words (although they do not mention this), in exactly that kind of physical environment which the epithelioid cells of growing, expanding tubercle must experience.

Let us suppose, then, that localizing tubercle bacilli stimulate monocytes *in situ* to the proliferation of epithelioid cells. The latter are confined within the surrounding tissue. As proliferation continues, and *epithelioids* multiply, the mass, especially its periphery, is subjected to increasing pressure, which packs the contained epithelioids more and more, and converts the outer ones to fibroblasts, thus establishing the *Anlage* for the later fibrous transformation of the tubercle.

As for the lymphocytes, and other minor cellular constituents of early tubercle, it is plain that they are cells which have "wandered" into the tubercle from the neighborhood and from nearby blood-vessels. They appear first at the margin of the tubercle, where they are always most numerous, and gradually make their way throughout the mass.

Why the Tissues React to Tubercle Bacilli with Nodular Tubercle: Primary Function of Nodular Tubercle

We come now to a consideration of why, natively, the tissues react to tubercle bacilli with their peculiar proliferation of cells *in situ*, which serve to invest the bacilli and form what appears to us as nodular tubercle. The answer to this question is, no doubt, to be found in the well-recognized circumstance that animal tissues deal in *essentially* similar manner with all substances with which they come in intimate contact, and which they are not equipped to absorb or dissolve, or to disintegrate in any other way. Dead tubercle bacilli arouse the formation of anatomical tubercle; so do all inert and nonbacterial (and therefore noninfectious) particles of high physical stability and insoluble constitution.

With tubercle bacilli we can even extract the component which is responsible for the formation of nodular tubercle. It is, as is well known,

the highly resistant wax in which tubercle bacilli (and other acid-fasts) are so rich. Injected alone, it will cause the production of nodular tubercle. Other bacteria contain similar lipoid substances (*vide* Ray and Shipman, *Amer. Rev. Tuberc., 1923, vii, 88*), yet do not cause the formation of tubercle because the lipins are a relatively minor constituent, and are too small in amount. But, when lipins constitute so great a proportion of a bacterium as is the case with acid-fast bacilli, they become a significant substance for the bodily economy to dispose of; and, without other more direct resources of attack, the tissues treat them as they would any other foreign body; that is, wall them off with tubercle and set them apart from normal tissues.

Tubercle, therefore, is to be viewed as the body's response to the fats, the lipins, the waxes, of the tubercle bacillus. Confronted with waxy microörganisms the body deals with them as it would with any other refractory substance. In forming tubercle, it exercises its constitutional capacity to deal with foreign particles in general.

Summary of Morphological and Functional Relations of Early Nodular Tubercle

In summary, then, nodular tubercle is the characteristic native response of the body to a foreign body introduced into the tissues. The foreign body concerned is the highly resistant wax of the tubercle bacillus; the tissue elements are cells existing *in situ* (monocytes?), which proliferate to form aggregations, the so called elementary tubercles around tubercle bacilli. Other ordinary constituent cells are wandering cells, leucocytes, especially lymphocytes, etc., which enter the tubercle from the outside. As external pressure upon the expanding mass increases, the epithelioid cells take on the characteristics (functions) of fibroblasts, capable of originating an investing fibrous tissue. Functionally, nodular tubercle is, at bottom, conservative and protective; it serves to wall off tubercle bacilli and limit their activities within the body in so far as it succeeds in localizing the bacilli and impeding their freer extension.

The Beginning of Allergy and the Conditions Necessary for Its Existence

Having carried our primary nodular tubercle up to about the third week after inoculation, we now enter upon a phase in the evolution of tuberculosis, in which other changes, specific and profound, are set up in the body by the tubercle bacilli present. By this time *tissue allergy* will be coming into full play. Sometimes detectable as early as the fifth day after very large first infections, it ordinarily becomes well

expressed at from ten to twenty days after the customary inoculations of experiment.

The *allergic state* (*tissue* allergy) in tuberculosis is, as is well known, a concomitant of the establishment of focal tubercle, be the latter the product of tissue reaction to living or dead tubercle bacilli. The smallest number of *living* bacilli, if they survive in the body, will infallibly lead to tissue allergy; and, with certain well-understood reservations, allergy will persist as long as bacilli remain. The intensity of allergy rises with the extension or progression of a tuberculous infection, or with any addition (for instance, from without) to it; it wanes with the subsidence of infection, as manifested by increasing fibrosis of foci, or by their healing, cicatrization and disappearance. To reach and maintain a given level of allergy requires the application (inoculation) of many more dead than living bacilli.

The *allergic reaction* (*tissue* allergy) is evoked by the contact of living or dead tubercle bacilli, or of dissociated protein derivatives (tuberculins) with the tissues of tuberculo-allergic animals. Available evidence would indicate that, while all tissues of the tuberculous animal are allergic, their degree of allergy varies. Pending decisive experimentation, we would hazard the opinion that in the same tuberculous animal the tissue that is most *hypersensitive* or allergic is that of the tuberculous foci themselves and the tissue in immediate proximity to foci; then the noninvolved (not actually tuberculous) tissue of those organs in which foci reside; and, last, the tissues of organs unaffected by tubercle.

Tuberculous animals are also allergic to *nonpathogenic acid-fast bacilli and their protein derivatives;* and animals with foci set up by nonpathogenic acid-fasts are allergic to tuberculin. But these *group-sensitizations* and *group-reactions* require several or many times the amounts of antigen that will induce species effects. Nevertheless, *group-specificity* among the acid-fast bacilli is a very real and sharp phenomenon, with implications that have barely been investigated.

All of the numerous reports of the production of allergy without the instigation of anatomical foci of tubercle have thus far failed of confirmation in competent hands or have been brought into question by other capable investigators. The latter are in agreement only on the circumstance that focal tubercle is accompanied by allergy. Accordingly, at the present time we may take the position that *all animals with tubercle acquire allergy, and tuberculo-allergy does not exist in the absence of focal tubercle.*

The General Anatomical Manifestations of Allergy

The most obvious features of tissue allergy are its anatomical manifestations; indeed, the allergic state is recognizable only through the occurrence of the allergic reaction, and the allergic reaction is made evident only by a series of characteristic tissue changes.

The essence of allergic reactions is *exudation*, appearing as typical *inflammation* in solid tissues and *effusions* in serous spaces. If the skin of a tuberculous, and therefore allergic, animal is injected with tuberculin or inoculated with tubercle bacilli (in the latter case reinfection will have occurred) the spot will become red and tumid within a few hours, with increase of local heat. If the dose of antigen has been large enough, the acute inflammation may go on rapidly to necrosis, apparent at times as early as twenty-four hours after injection; if it is on the surface, the necrotic patch may slough, and an ulcer be formed. In very violent allergic reactions, a haemorrhagic necrosis may result. Second and later inoculations of tubercle bacilli into the thorax or abdomen will give rise to serous, purulent, and even haemorrhagic effusions, always developing rapidly, although primary infections with similar "dosages" of bacilli had been without any visible effect for days. Bacilli of reinfection, introduced intravenously and settling in the lungs, will cause the formation of patches of pneumonia and petechiae of variable size, frequently prominent within twenty-four hours. Repeated observation of the cut-surface of such lungs will often disclose the pneumonic areas passing through the several stages of hepatization. Microscopic examination will show that *for a few days* after reinfection the tubercle bacilli lie at or near the centre of fields which are characterized by an outpouring of leucocytes, red blood cells and serum, and often a desquamation of epithelium into the alveoli, while, except for the oedema caused by exuded serum, the interstitial tissue (septa, etc.) shows no changes, and is intact.

It is plain that in the allergic reaction we have a process which gives rise to *non-nodular* or *diffuse* anatomical tissue responses to tubercle bacilli (or to tuberculins). We are now permitted to regard all inflammatory features of tuberculosis as expressions of *tissue hypersensitiveness*, and as representing reinfection, which, of course, includes metastasis or extension of already present infection. Therefore, all clinically acute tuberculosis but reflects allergic tissue response. Tuberculous pneumonia and tuberculous effusions (pleural, peritoneal, meningeal, articular, etc.) are always the result of the allergic reaction.

When, as in experiment, single moderate applications of tubercle bacilli are employed by way of reinfection, the acute inflammation at the site of inoculation may subside rapidly, especially if it has not been so severe as to cause sloughing and ulceration. Within a few days the affected part returns practically to normal. And now we find, arising out of the spot but recently given over to acute inflammation, a nodular tubercle with the essential characteristics of that nodular tubercle with which tissues respond natively. But, properly controlled experimentation will reveal several significant differences between this tubercle of reinfection and that of first infection. For one thing, this tubercle in the allergic animal appears a little earlier than does tubercle called forth by similar inoculations (dosage, etc.) in the animal of first infection. Again, it runs an abortive course, reaching its acme earlier, and then retrogressing and perhaps disappearing,—all this without ulceration if "dosage" of reinfecting bacilli has been moderate.

When the acute inflammation of allergy has been severe enough to eventuate in ulcer the latter may rapidly close over and heal, frequently permanently, and sometimes with a later development of small and rather abortive nodular tubercles in the affected area.

The significant anatomical features of the allergic reaction may therefore be assembled as follows:

First: The response of the tissues to tubercle bacilli is *exudative*, as contrasted with the native response of proliferation; the effect is an inflammation; and the visible result is a *diffuse* formation, again as contrasted with the nodular *circumscribed* structure of native anatomical tissue response. Since we never meet with inflammation in tuberculosis except in the allergic animal, we may proceed to the assumption that all inflammatory features of tuberculosis are allergic.

Second: The inflammation of allergy develops with amazing rapidity; visible anatomical effects are in this respect in striking contrast with those that follow primary infection and appear as nodular tubercle.

Third: In the allergic animal new nodular tubercle of reinfection itself develops more promptly than in the animal of first infection. (*Vide* Krause and Peters, *Amer. Rev. Tuberc., 1920, iv, 551.*)

Fourth: Foci of tubercle existing in the body at the time of reinfection may also undergo acute inflammatory allergic reaction, and, as a result, have their fibrosis markedly stimulated.

Necrosis (Caseation) Is a Resultant of the Allergic Reaction

Although a discussion of the degenerative processes of tuberculosis,—of necrosis, caseation, suppuration, etc.,—belongs more properly in the preceding section, we have preferred to set them apart for separate consideration, because of the conflicting and frequently bizarre opinions held as to their nature and origin.

Some authors have looked upon the necrosis (caseation) of tuberculous formations as due to the direct effects of a peculiar and specific poison of the tubercle bacilli. When confronted by the failure to demonstrate *toxins* for tubercle bacilli, and by other circumstances that would suggest the nonexistence of such substances, they have shifted their ground to the predication of so called "endotoxins" as the agents of tissue death. "Endotoxins," as *inherently specific* poisons, must be regarded as purely hypothetical constituents of a microörganism; and in the circumstances "endotoxins" have never enjoyed any more real existence than this designation of them as an imagined substance to account for an effect observed.

Impressed by the obvious avascularity of tubercle and the thrombosing action of the tuberculous process in general, other authors have ascribed the necrosis of tuberculosis to tissue ischaemia. The peculiar character of the necrosis of tuberculosis, the *caseation*, which is frequently not unlike the appearance of anæmic infarct, has served to lend color and a certain superficial plausibility to such a view. But, the critic would ask why, then, the most minute, even microscopic, tubercles may undergo necrosis at their centre, although they can hardly be imagined to be cut off from sustenance present in abundance only a microscopic distance away. Again, caseation in the lung and liver, for instance, is characteristically the same cream-colored necrosis as anywhere else, yet pulmonary and hepatic infarcts, for well-understood reasons, are characteristically red.

There have been some who would deny to tubercle bacilli any part in the production of necrosis and pus in tuberculosis. They have set the tubercle bacillus apart, as incapable of originating pus, and have called upon the more common pyogenic cocci as being responsible for the more destructive features of tuberculosis. It has been maintained that even acute inflammation is beyond the purview of the tubercle bacillus, and that all inflammatory phases of tuberculosis arise from the associated activities of so called secondary invaders,—microörganisms which (in their opinion) commonly make of tuberculosis a "mixed infection."

Now, that bacteria other than tubercle bacilli maintain a residence in tuberculous foci need not be questioned, although the postulate still awaits absolute proof. It would be surprising if numerous old foci of as chronic an infection as tuberculosis did not take to themselves micro-organisms of many kinds in the course of years. Yet, it should be unnecessary to point out to this audience that the mere presence of germs, pathogenic or otherwise by nature, is no evidence of their setting up a disease, or contributing to it anywhere. As to the facts of the case, we again and again find necrosis and abscess-formation in tuberculosis under conditions in which the activities of bacteria other than tubercle bacilli never come into question; in the ordinary cold abscess, for instance, or in renal tuberculosis. Instances of the latter are to be observed, which can be regarded almost as classical examples of tuberculous abscess, and in which the bacteriological findings are extraordinary numbers of tubercle bacilli and complete absence of other germs. Or, we are reminded of spontaneous pneumothorax, arising preponderantly on a basis of tuberculosis, and, often as not, through the rupture of a diseased pleura overlying an old pulmonary cavity,—the ideal situation, if any, for "mixed infection" to thrive. Yet few are the cases in which spontaneous pneumothorax *begins* with any bacteria other than tubercle bacilli detectable; and we again remember that the tubercle bacillus is a slow-growing germ, and that the alleged "secondary invaders" multiply much more rapidly, and should overgrow and obscure the former if they played any significant part in the infection and the anatomical process. Of course, like any other person, a patient with tuberculosis may get pneumonia or influenza or a common "cold," or any other respiratory disease. But such events are not germane to the present discussion, and do not enter into our concepts of "mixed infection."

But, aside from all argument by negation, the truth is that an idea of necrosis and suppuration in tuberculosis being caused by bacteria other than tubercle bacilli has little to support it save reasoning by analogy to supply what were once gaps in a confused and insufficient comprehension of the pathological anatomy of tuberculosis. As has been said elsewhere, the idea "is really nothing more nor less than the old dualistic doctrine revamped in a new guise and refurbished to meet the necessities of a modern bacteriological point of view." And, surely, as we observe, under unexceptionably controlled conditions, the effects of the allergic reaction, we do not have to look further for the cause of necrosis in tuberculosis. Surely, every one with only passing knowledge of tuberculosis knows by

this time that *tuberculin is necrotizing for the tuberculous, that is, the allergic animal.* So are tubercle bacilli necrotizing for the tuberculous allergic animal. And the necrosis, when its evolution is subjected to the test of experimental control, will always be found (when it occurs) to be *an* end-result of the inflammation with which the allergic reaction is initiated.

With Allergy Established, All Present or Future Tubercle Is Structurally Modified by It

With the establishment of the allergic state in an animal, it must happen that, from that time on, every nodular tubercle then existing in the body will continue its evolution under the influence of allergy, and that every new formation which arises in response to a fresh localization of bacilli will from its very inception be modified in its development by allergy. The structural results will be significant, and often profound, and, not rarely, decisive and unique. From now on we must regard all tissue formations aroused by tubercle bacilli as pursuing, at all times, a cycle which is determined by the combined effects of the body's native compulsion to respond proliferatively with nodular tubercle and of its newly acquired property to react exudatively with inflammation and the latter's end-results, namely, with resolution or with tissue death and destruction. Frequently, proliferation and its accompaniments will be dominant; frequently, inflammation and its sequellae: it is quantitative relations,—of intensity of allergy, of "dosage" and distribution of bacilli, of concentration or dispersion of localization,—that will sway the balance and mould the issue. But, however complex the final structure, however obscured by detail may be its fundamental nature, every formation originated by the activities of tubercle bacilli will have been the resultant of one or several or all of only four basic processes. Primary elementary tubercle, pneumonic or cheesy patch, ragged pulmonary cavity, pleural effusion, fungating joint, fistulous tract,—into the formation of each and every one has gone, either individually (which must be exceptional) or together or seriatim in variable proportions:

1: Proliferation, the essence of native tissue response.

2: Exudation, the essence of allergic response.

3: Necrosis, an anatomical end-product of inflammation (exudation).

4: Fibrosis, an anatomical end-product of proliferation, and, no doubt, also of the inflammation of allergy.

The Structural Evolution of Primary Nodular Tubercle Continued

With the above forces in active operation the tissues now proceed to build up tuberculous structures, such as we have come to know them, and are accordingly familiar to us.

First, let us again take up the further evolution of our primary nodular tubercle, which, it will be remembered, we left just as it was completing what was called its pre-allergic phase.

The nodule was losing its nicely rounded contour. The zone of skin immediately embracing it was turning pink, as was also the outer part of the hemispheroid of the tubercle; and the latter's centre was becoming whitish and opaque as, at the same time, it began to be less firm to the touch. Perhaps minute, pale, firm nodules were just coming to view in the surrounding rim of pink skin, and this rim, taking on now a slightly irregular outline, was losing its normal softness and presenting the recognized signs of induration.

As was mentioned, we are now in the third week after inoculation. We test the animal with tuberculin (on its other side) and elicit a vigorous inflammatory reaction. We are thus made certain that its tissues are allergic; and, knowing this, we can understand the structural changes going on under our eye.

At its origin, this nodule was a mass of proliferated cells enclosing tubercle bacilli. The bacilli have remained alive, and have multiplied, and some of them, quite likely a very small proportion, have been moved from the centre of the mass to its more peripheral parts, and even out of the mass into the zone of skin immediately surrounding it. The tissues of the body are now allergic and the tubercle is allergic. All bacilli are now residing, are living and dying and multiplying, in allergic soil. Wherever they have settled and are settling, antigen is being released. Wherever this is in sufficient amount, the signs of inflammation are becoming visible; hence the change to pink at the periphery. Wherever antigen is in still greater amount, but an amount which must, of course, be enough for the purpose, necrosis comes upon the tissue; hence the yellowish, opaque point of softening at the centre; it is here where *during the first few weeks* the bacilli of every tuberculous focus must be most numerous. Fibrosis is now going on apace at the margin of the tubercle; hence, the increasing induration there. And the very small pale nodules in the surrounding pink skin are new daughter tubercles, minute and abortive, and springing up in the sensitized tissue from bacilli moved there from the parent mass.

Recourse to the microscope will confirm this naked-eye appraisal of

structure. A circular aggregation of epithelioid-cell masses is now marked by central necrosis and a definite fibrous investment. Infiltrating leucocytes are a prominent feature, and form a veritable film around the tubercle. They are mainly of the lymphocytic order. A few tubercle bacilli may be seen in the mass out near the periphery, besides a more numerous collection becoming involved in the central area of necrosis. And just outside the main tubercle itself are one or a very few new and smaller tubercles developing around several tubercle bacilli.

This primary tubercle now presents, in epitome, and in full evolution, all features which enter into the structure of every tuberculous formation that holds to the nodular type, however extensive such a formation may turn out to be; that is,it does so up to the time of loss of tissue. And, as it continues to evolve, it will display another significant combination of circumstances. This is, that in the normal cycle of development of tubercle, the structure always undergoes necrosis and fibrosis *at the same time;* and, what is of great importance, that necrosis begins at the centre of tubercle and proceeds from here outward, while fibrosis always starts at the periphery, whence it extends inward. If central necrosis keeps pace with and outstrips peripheral fibrosis, the tubercle is pathologically progressive. If peripheral fibrosis extends inward and encroaches the while upon central necrosis, the tubercle is pathologically retrogressive. Continued or extending necrosis is contingent upon the survival of interned bacilli and upon their multiplication. The latter have sensitized (allergized) the tissues of the tubercle *in situ.* As they live and increase, some of them also die, and in disintegrating yield up their antigen, to necrotize the tissues if the antigen is in sufficient amount. Multiplying, the bacilli are moved gradually peripheralward, and little by little have their antigen released, to extend the zone of necrosis; and the latter begins to affect even the new-formed fibrous tissue which has been reaching inward.

The Formation of Larger Nodular Tubercles

But only rarely could such a tubercle, with necrosis crowding upon and wearing away its fibrous investment, retain its small and isolated character. Advancing necrosis, as has been mentioned, mirrors multiplication and activity of bacilli. The range of these will be extended. Where descendant bacilli of the parent focus settle, new tissue reactions will greet them; and, as long as their numbers at individual points of fresh

localization are small, the result will be nodular tubercle (modified by allergy). Accordingly, new foci will appear within the outer fibrous layers of the parent tubercle itself; or (and), as is usual, outside the latter, yet perhaps nearby, just as we saw them appearing in the border of our primary skin tubercle. Both parent and daughter tubercles, if they progress, will enlarge their mass. Fibrosing boundaries will come into contact, and, in time, will coalesce. From a single small nodular tubercle, there will now result a larger composite tubercle.

Such a development of a greater from a lesser formation represents one method by which large nodular tubercles are built up. The process requires conditions that make for a comparatively indolent growth of tubercle bacilli, and, consequently, more tardy development of tubercle, and the conveyance of relatively few bacilli to points close to the parent tubercle outside. Short excursions are made by lymphatics, as a rule, in this type of extension. When few bacilli are carried a little further away, yet are deposited fairly close to the parent tubercle, the daughter tubercles may long remain discrete. Since the bacilli concerned were never numerous, caseation is not particularly pronounced. The whole process for years may be one mainly of fibrosis, and therefore with chronicity dominant. And we arrive at an anatomical *ensemble* of several or numerous fibrocaseous, though mainly fibrous, tubercles, set separately, though never far apart. This condition is exemplified in that most common of types of human tuberculosis which we designate clinically as *chronic infiltrating tuberculosis of the apex* (of the lung).

But there is another way in which, very frequently, the larger nodular types of tubercle are built up. This is through the conjunction and coalescence of several or many individual tubercles that have originated close to one another from bacilli derived perhaps from a common source. Some older focus erupts and discharges its contents into, say, an air-passage. Bacilli are deposited at or near the termini of a bronchiole at several separate yet adjacent points. If the numbers of bacilli at each *locus* are not too great, several nodular tubercles will result. These, in growing, join, and form a single irregularly rounded mass.

At a comparatively early stage of its development the cut-surface of such a mass is singularly characteristic. It presents a mosaic of translucent or pearly circles of grayish lines, within the centre of each of which is a minute opaque yellowish dot. In other words, the boundaries of the individual component tubercles are still visible, marked out as they are by orbicular strands of fibrous tissue, while, within, each shows the

central spot of necrosis. If such a compound tubercle continues its progressive cycle, the interior intervening lines of fibrous tissue will be wiped out by the extending necrosis, as the several spots of the latter blend into a single necrotic mass. Meanwhile, the external peripheral arcs of fibrous tissue will become a single fibrous investment for the whole mass. When this happens, all earmarks of the original constitution of such a tubercle will have been obliterated; and the cross-section appears as a single orb of caseation set within its fibrous ring.

Fibrosis

Fibrosis is so important an element in the structure and function of tubercle that it may well deserve separate comment at this place.

As we have seen, the beginnings of fibrosis are to be made out in the earliest stages of tubercle-formation. In the smallest nodules the outermost layers of epithelioid cells are to be seen apparently to take upon themselves an arrangement and a laying down of fibrils which results in the nucleus of an investment of the mass. It can hardly be doubted that minimal epithelioid reactions to very few bacilli, which soon die, never undergo central degeneration and necrosis, and are resolved and disappear. Such tubercles must be very frequent. It would also appear as though tubercles of more advanced evolution, after suffering a certain amount of caseation, experience some resolution of even their young fibrous tissue; for it has been observed that such tubercles also fade from view, and, if they leave any trace, this must be a microscopic fibrosis.

But whenever there has been any measurable death and destruction of tissue, some scar, however slight, must presumably result. And, as has been described, fibrosis always begins at the periphery of tubercle and extends from here inward. In time, then, every such tubercle will come to have a greater or less part of itself made up of fibrous tissue. This tissue will take the form of anything from a capsule of variable thickness and density to a fibrous mass which completely replaces the structure of the tubercle.

Fibrous tissue is undoubtedly derived from other processes than through the fibroblastic conversion of epithelioid cells. It is laid down also as an end-result of the inflammation of allergy. After primary tubercles are established, as well as from the time of origin of secondary tubercles, all such formations are set in a zone of inflammation of the utmost variability,—a variability that is contingent on the amount of

bacillary products (bacilli) which can make their way out of the tubercle and react with the surrounding tissue. Density and thickness of the focal envelope will, obviously, be potent factors in determining such quantitative relations. Therefore, it must happen, as in the case of all inflammations, that peripheral fibrosis is stimulated and added to by these continued low-grade marginal inflammations with their recurring exacerbations. During the life of a tubercle, that is, while it is still in active anatomical evolution, peripheral fibrosis is thus made denser, and the thickness of focal investment is also increased to some extent by extension outward.

In a way, the entire interrelationship between infected body (tissue) and focal interior depends upon the character of the fibrous investment of tubercle. This stands between bacilli and poisonous focal products contained within the tubercle, on the one hand, and the bodily economy on the other. Through it must pass substances from the tissues to nourish the bacilli, and materials and bacilli from the focus to affect the body. *Thoroughly avascular itself*, tubercle can communicate with the surrounding tissue only through the intermediation of tissue lymph. And, from the point of view of structure, it is the density and thickness, the compactness and competence, the perviousness or imperviousness, of the focal envelope which will regulate this interchange. The clinical history of the ordinary case of pulmonary tuberculosis records largely the changing character of the focal investment of the tubercle present; or, as it is sometimes put, the nature of a focus is generally much more momentous than its extent. By "nature" in this connection, we usually think of its character as regards fibrosis.

The Development of Nodular Tubercle Summarized

Accordingly, in their development, all nodular tubercles, large or small, represent circumscribed tissue masses, undergoing a mixture of proliferation and exudation, and the end-results of these, necrosis and fibrosis, in illimitably varying proportions; while the masses themselves are surrounded by tissue usually in low-grade inflammation (as long as focal investment is not too tenuous) but subject to acuter exacerbations until the fibrous wall is completely "tight." The inflammatory features are allergic; so is tissue death; so is the perifocal zone of inflammation. Fibrosis is also stimulated by the slight inflammations of countless mild perifocal allergic reactions. It is the severe ones which, before their subsidence, may lead to trouble; as *vide* violent focal tuberculin reactions,

which can "unlock" previously satisfactory investments and lead to acute necrosis of foci and release of focal products (bacilli) to the outside. The fate of any particular focus will turn on the issue between necrosis, with its outward thrust, and fibrosis, with its counter-force. Larger nodular tubercle is evolved from the concentric growth of small tubercle, or from the gradual approach to one another of separate tubercles and their ultimate coalescence.

The Last Phases in the Cycle of Nodular Tubercle: Ulceration and Excavation

The story of the rest of the cycle of nodular tubercle is soon told. As has been intimated, the process of tubercle-formation can stop at any point, and the part affected return to normal; or the tubercle can be completely converted into fibrous tissue; or it can remain for a long time, perhaps permanently, a fibrocaseous nodule, seen on cross-section as a globule of necrotic tissue enclosed by a fibrous capsule, the latter usually very compact and thick, and at times almost cartilaginous. Or, the necrotic tissue may have been replaced by calcific material, deposited from out of the body fluids, in which case a stony concretion (*pneumolith, broncholith*) is held within the tightly fitting fibrous envelope.

But if the cycle continues and death of tissue progresses, the once rather firm necrotic material begins to disintegrate and crumble, and take on a semifluid or fluid character. With a tubercle whose investment remains intact, such debris may be disposed of by cells of leucocytic type, which, in the circumstances, enter the tubercle in large numbers and act apparently as "scavengers." Gradually a loss of tissue occurs, and we have a space or *cavity* within a closed tubercle.

In the lungs excavation goes on much more frequently in tubercles that are in communication with air-passages. Central caseation comes to extend to the very margin of the tubercle, and proceeds to involve the walls of adjoining bronchi (bronchioli). It at last breaks through the bronchial surface, just as we saw it in our primary skin tubercle; and an ulcer forms. As tissue death within the tubercle continues, the detritus and liquefied pus is discharged into the bronchus, and the tubercle is now well on its way to the formation of cavity. As tubercles come into relation with the air-passages, the sensitized tissues of the latter become locally inflamed, and, even though the tubercle has not ulcerated, they suffer catarrh or more severe inflammation, according as their allergic reaction to neighboring tubercle is more or less marked. Just before, or

after tubercle has ulcerated, the air-passage of discharge may itself be involved with fresh tubercles, which develop at first in its submucosa. Thus the bronchial changes are aggravated, and the local symptoms correspondingly so.

After a necrotizing tubercle has found a vent, as it were, through ulceration into an air-passage, the result is not dissimilar to that achieved by the surgical evacuation of any abscess. Conditions are now much more favorable for an enhanced peripheral fibrosis than they were when the latter was menaced by the full influence of the confined bacilli and necrotizing tissue. Therefore, such cavities are prone to develop very dense and thick walls. Yet, on their internal surface bacilli may continue to live on, and little by little bring about the death of tissue, which sloughs off and leaves a shaggy cavity lining. Abiding in a state of allergy and chronic inflammation, such cavities go on for years, with their walls being gradually worn away within, and being compensated for this loss by a continual accretion of fibrosis, which keeps enlarging the boundaries of the cavity and also contributing to the density of the wall. In time, such cavities arrive at that paradoxical state which we not uncommonly encounter clinically: a large cavity, secreting much purulent, bacilli-containing sputum, in patients without constitutional symptoms. It is plain that these cavities possess walls too thick and compact to allow the passage out into the tissues of enough poisonous material to affect the patient.

If the tuberculous process within a pulmonary cavity comes to a standstill and bacilli are completely destroyed, the cavity may be entirely replaced by scar tissue. This happens when it is not too large and its walls can be brought into apposition. Or, the cavity may partially remain, and its smooth inner wall secrete mucoid material permanently.

Diffuse Formations Aroused by Tubercle Bacilli

Very extensive nodular tubercle may, on section of such an organ as the lung, give one an impression of diffuseness; but closer examination will always show that it is circumscribed and definitely marked off from its neighborhood, whether the latter is normal or pathological (for instance, congested or pneumonic).

Non-nodular, really diffuse tissue reactions to tubercle bacilli are frequent. Indeed, it is doubtful whether any clinically active case of pulmonary tuberculosis can long be in a condition of clinical activity without experiencing them in at least a minor degree. They provide the

anatomical setting for all the more acute clinical manifestations of tuberculosis, from those familiar fulminating spurts which last only for the day to those better-defined episodes of weeks and months of continuous or remittent fever, which we dignify with distinct clinical classification.

We have already paid attention to the forces responsible for the diffuse tissue reactions to tubercle bacilli in our section on *The General Anatomical Manifestations of Allergy*. Allergy underlies all of them, and the allergic reaction, inflammation, is their prototype. Therefore, before they may fall upon the tissues, tubercle must have been established and must be at work somewhere in the body. Therefore, they represent tissue response to reinfection,—to metastasis or extension of preëxisting foci. And, by way of confirmation of this opinion, we have the easily ascertainable fact that in controlled experiment they are never obtainable except by the reinfection of tuberculous (allergic) animals.

Examples *par excellence* of diffuse formations provoked by tubercle bacilli are acute pneumonic foci in the lungs and effusions into the serous spaces. The former may involve only a few primary anatomical units, to give rise to an alveolitis that hardly produces symptoms and is not to be appreciated clinically; or they may suddenly overwhelm the greater part of a lobe, or even the whole lung (as, for instance, in *phthisis florida*).

The larger pneumonic foci, such as those which provide the anatomical background of the clinical disease, *acute tuberculous pneumonia*, require for their origin conditions which effect a high and rather sudden concentration of comparatively large numbers of tubercle bacilli within a tissue. We meet with ideal conditions for their production when considerable material is discharged abruptly from an upper-lobe focus and aspirated to points lower down, or when caseating foci in tracheobronchial lymph nodes break through and into the major air-passages. Clinically, therefore, the better and more pronounced cases of tuberculous pneumonia are located in regions below the actual summits of the lungs, although typical chronic pulmonary tuberculosis begins as apical disease. It is the latter which, in most instances, gives rise to the former.

In these diffuse tuberculous processes within the lung, there takes place a very rapid exudation of elements from the blood and a shedding of epithelium from alveolar walls throughout a field which may extend far beyond the actual point of localization of the newly arrived bacilli. The bacilli, if in a single depot, will be at the centre of the affected sphere of their action. The exudative process will be most intense in the im-

mediate neighborhood of the bacilli, and from here will "taper off" by degrees peripherally, until normal tissue again is reached.

The event takes place with great rapidity; so suddenly, indeed, that we must believe that anatomical changes would be detectable within, at the most, a few hours after the deposition of bacilli, just as the abruptness and other features of clinical onset may suggest a focal eruption only a few minutes before. The alveoli soon become engorged with the several exuded elements mentioned, while, at first, as has also been said, the interstitial tissue exhibits no changes except those of oedema.

At its beginning, the process may be as purely and as characteristically pneumonic as the ordinary effects of pneumococci or streptococci in the lungs. Gradually, also, it resolves, at least partially, proceeding from the periphery inward; and if the bacilli remain localized to their original central position, a large pneumonic patch may clear with fair rapidity throughout its more peripheral parts. More rarely, such a patch clears completely; but this can occur only if all central bacilli have been destroyed in the acute reaction, and have been disposed of.

As a rule, however, bacilli remain, and keep on exerting an influence that extends out into the neighborhood. At this nucleus of the original path of inflammation, nodular tubercle, with perhaps an enhanced tendency to both necrosis and fibrosis, will develop more promptly than usual, as was noted in the case of tubercles of reinfection in the skin of experimental animals. Contingent, then, on the survival and multiplication of the bacilli, this central tubercle-formation may long persist, and go through all the later changes described as possible for ordinary tubercle, and eventuate in cavity, or fibrocaseous focus, or fibrous scar.

When the bronchial metastasis to a spot is extreme, necrosis of considerable extent may strike the inflamed tissue even before nodular tubercle has come to view. There result nonencapsulated diffuse patches of caseation, which do not become invested until later. Such an effect may be compared with the rapid necrotization and sloughing that may attend a violent tuberculin reaction of the skin within two or three days after injection, or the inoculation of excessive numbers of tubercle bacilli into the skin of an already tuberculous animal.

In that rare disease, *phthisis florida*, extreme reinfection is diffused throughout a wide territory. Large numbers of tubercle bacilli are scattered almost everywhere. A whole lobe or lung becomes pneumonic at a stroke and *en bloc*. Many fields of diffuse necrosis soon intervene, and rapid disintegration of tissue goes on in them. Real nodular tuber-

cle is abortive. The cut-surface of such a lung may disclose numerous irregular areas of necrosis of a crumbling nature and with ragged clefts and gaps, out of which the disintegrating tissue has fallen; yet there will be little, if any, evidence of investment of these areas. Here we are gazing at fulminant and diffuse necrosis of acutely inflamed tissue.

If necrotized patches of diffusely inflamed tissue are not too extensive, they will become invested with fibrous tissue (or even replaced by it). But, whenever tubercle bacilli survive the reaction, nodular tubercle will soon enter the field and contribute to the general result.

Little need be said about tuberculous effusions except to insist that purulent ones in tuberculosis may be of tuberculous nature, and most frequently are so, until contaminated by repeated interference. The same may be said for abscess, as, for instance, psoas abscess. Indeed, with the exception of instances of renal tuberculosis, the writer has never seen so many tubercle bacilli alone in specimens as in a few cases of pyopneumothorax. Experimentally, we can uniformly obtain purulent pleural effusions by directly reinfecting the thoracic cavity of allergic guinea pigs with large numbers of tubercle bacilli.

Miliary Tubercles of Reinfection

While the term *miliary* is applicable to any discrete tubercle of well-understood size and to any pathological change in which collections of such tubercles are the outspoken feature, we prefer to use it here to designate those small discrete tubercles that result from a widespread seeding of material from a focus discharging into a major channel of dissemination.

Numerous separate tubercles of limited though uniform size then arise throughout an organ. The infection has obviously been one of reinfection, that is, metastasis, and must have taken place in allergic soil. Accordingly, one wonders why so frequently at autopsy of the case of miliary tuberculosis, the tubercles are marked by so few or slight evidences of acute inflammation.

There are two main reasons for this circumstance. The first is that the time between the infection, that initiated the miliary tuberculosis, and death is usually so long that whatever acute inflammation originally occurred has subsided in the interval. The second reason is that the numerous individual fields of inflammation are, from the beginning, comparatively limited and mild.

In the case of the acute pneumonic patch, which we encounter clinically

as tuberculous pneumonia, much focal material (bacilli) has been concentrated within a limited compass; and the visible result is compacted and intensified in its vigor and violence. But, in the case of generalized miliary tuberculosis, much focal material is dispersed to very many scattered points. Every individual point receives only its small fraction of the original quantity of bacilli. The individual allergic reactions (inflammations) are therefore anything but intense and extensive, although the sum total of effect,—which the patient feels,—may be considerable enough to render him acutely ill. The two or three, or score of bacilli that settle out to call forth each miliary tubercle will evoke but mild and rather fleeting acute inflammations at each single place, just as similar numbers of virulent bacilli will act in the most highly allergic animal of experiment. And in each spot there will soon afterward evolve each miliary tubercle, a little more promptly and a little more abortive than if the soil had been that of a nontuberculous person.

As a matter of fact, for the first week or two after comparable experimental infection of an animal, these focal inflammatory changes are pronounced enough.

Recapitulation

Let us now recapitulate: as we pick up these many scattered threads that go into the making of tubercle, and attempt to weave them into the meaning of structure as a whole—its origins, its forms and its functions.

There are microörganisms, tubercle bacilli, which, for reasons thoroughly unknown to us, can live and multiply in the bodies of certain animals, of which man is one.

These microörganisms are sluggish in development, but hardy of constitution and tenacious of life.

Their hardihood and their resistance to outside agencies are undoubtedly the consequence of their possession of an extraordinarily high constitutional content of lipoid substances, of which a very refractory wax (or waxes) is in greatest abundance.

They are also endowed with protein (or proteins), combined peculiarly, no doubt, with their wax.

When, living, they settle in the body for the first time, the tissues react to their presence by forming nodular tubercle. The tissues form nodular tubercle because they react in this way to the *lipoids* of the bacilli. Nodular tubercle is their native method of dealing with those refractory sub-

stances, so called foreign bodies, which they cannot dispose of by direct disintegration and dissolution.

Nodular tubercle, at bottom, is therefore a protective and conservative process, serving to wall off tubercle bacilli and set them apart from normal tissues. In by far the greatest number of tuberculous infections, the ninety per cent and more which never become active clinically, nodular tubercle performs this defensive function successfully, as it keeps in confinement tubercle bacilli and the other deleterious products of its interior (such as degraded proteins of component cells).

Nodular tubercle evolves slowly out of the proliferation of cells *in situ*. It is a circumscribed process.

With the presence of tubercle bacilli in the body, as represented by the establishment of nodular tubercle, the tissues acquire a new and added method of reacting to tubercle bacilli.

This new capacity of tissue reaction is to the *proteins* of the tubercle bacilli.

The changed conditions of the tissues is called *tissue allergy* or *tissue hypersensitiveness*. The reaction elicited by the proteins of tubercle bacilli is the *allergic reaction*.

The allergic reaction brings about non-nodular diffuse tissue changes. It is characterized by a rapid exudation of cellular elements from the blood to form acute inflammations and effusions.

At bottom, tissue allergy is also a defensive and conservative process. Through prompt inflammatory responses it serves to stay the more facile progression of tubercle bacilli that takes place in the body of the normal, nonallergic animal. It fixes bacilli where they lodge much more capably than does *early* nodular tubercle. However, in accomplishing this function it renders animals acutely and often dangerously ill. After infection has been accomplished, it serves as the body's chief instrument against the unrestrained dissemination of infection that would otherwise attend the frequent catastrophic eruption of foci, or the ordinary mobilization of variable numbers of bacilli from foci. The inflammatory allergic reaction also tends to stimulate greatly the powers of nodular tubercle to form fibrous tissue; and thus sets the stage for abortiveness and chronicity of tubercle-formation after the more acute phases of inflammation have passed.

The tissues form nodular tubercle around inert, nonbacterial foreign bodies. They treat the extracted lipoids and dead tubercle bacilli in

the same way. Structurally and anatomically such a result constitutes tuberculosis. But, aroused by lifeless *agents provacateurs* it is an inert tuberculosis, lacking the power to expand, erupt and spread, the prime attributes necessary to render tuberculosis momentous.

Alive and reproductive, and able to continue thus in the body, living tubercle bacilli make of the tuberculosis, which they call forth, a parasitic invasive graft, instinct with potentially unlimited powers of extension and progression.

When animals become tuberculous, their allergic tissues respond to the dissociated proteins of tubercle bacilli (tuberculins) with acute inflammation and its sequellae (necrosis and fibrous-tissue stimulation). Their tissues deal with dead tubercle bacilli similarly. Anatomically, both tuberculins and dead tubercle bacilli evoke the diffuse formations of tuberculosis. These diffuse formations are essentially similar to those derived from living tubercle bacilli.

Accordingly, with dead tubercle bacilli, correctly applied as regards requisite conditions of mass and time, we can reproduce in experiment all basic features and types of structure familiar to us as the effects of living bacilli.

Tuberculous formations may be looked upon as being composites of the effects of the lipoids and proteins of the microörganism concerned. The *disease* tuberculosis is based upon the extension and progression and repetition of tuberculous formations. The essential difference between the disease tuberculosis, caused by living bacilli, and a state of tuberculous formations set up by dead bacilli is to be found in the capacity for continued and indefinite development and multiplication of tubercle inherent in living bacilli. These provide conditions for the indefinite multiplication and growth of foci, and for the periodic or continuous *progressive* involvement of foci by destructive processes, such as necrosis and cavitation, which are contingent upon sufficient quantities of antigen (protein) released by tubercle bacilli flourishing and disintegreating within the foci.

In their normal evolution all tuberculous structures come to represent a mixture, in varying proportions, of the effects of nodular tubercle-formation and allergic inflammatory reaction.

Larger nodular tubercles are built up mainly from the coalescence of smaller ones. The cycle of all tubercles is, to a variable degree, predetermined by whether they originate in allergic or nonallergic soil.

The ultimate issue of every tuberculous focus turns upon the balance struck between central necrosis and peripheral fibrosis.

Necrosis of tubercle is a result of allergy,—a sequel of the inflammatory reaction. It begins centrally and extends outward.

Fibrosis is brought about through the conversion of epithelioid cells of nodular tubercle into fibroblastic types. It is greatly enhanced by the allergic inflammatory reaction as the latter subsides. It begins at the periphery and extends inward.

From the point of view of the bodily economy the most important single element of tuberculous processes is the integrity and competence of their fibrous investments. These stand between interned bacilli, available otherwise to arouse new foci outside, and the body. They also stand between poisonous focal products and the body, which would otherwise be affected.

The ideal of therapy is, of course, a practicable bactericide. Meanwhile, as we await this, it would appear that a study of structure would suggest the following paths as worthy of exploration:

1: That directed toward the discovery of a medium or method to accelerate and heighten cellular proliferation and fibrosis. Dangers lie in enhancing the tendency of tissues to tumor-formation.

2: That toward a medium to neutralize the intoxicating products of the allergic reaction. If it were nonspecific, it might prove a veritable boon in many infectious diseases.

3: That toward a medium to neutralize the poisonous products that proceed from tuberculous foci. For reasons frequently expressed, it is believed that these are not specific, but are substances that result from the death and disintegration of the cellular components of foci. Can a substance antagonistic to them be found? Or a substance that would so act upon the body as to ward off their physiological effects? To abate or control the constitutional symptoms of chronic pulmonary tuberculosis would be an enormous advance, even though the anatomical process were not directly influenced. To-day we aim at the fibrous investment of tubercle, striving to strengthen it. Our methods, imperfect though they are, continually do wonders. May we not also look forward to supplementing these with measures directed against the focal contents of tubercle, or, less empirically than at present, against the symptoms these engender?

THE ONSET OF TUBERCULOSIS IN MAN

LÉON BERNARD[1]

I

When we speak of the onset of tuberculosis this suggests to the minds of physicians the idea of the beginning of the evolution of the disease in the adult, and the necessity of detecting it at an early stage.

As a matter of fact we shall not deal with this point of view in our address. This so called onset of tuberculosis in the adult is not the beginning of the disease; it is merely a revival. The real beginning of tuberculous infection does not take place in the adult at the time of the appearance of its so called early manifestations, for much time has usually elapsed since the individual became infected; the infection occurred in childhood and became, so to speak, deeply rooted.

Behring was the first to point out this fact definitely. His discovery was followed by a considerable amount of research work in all countries, which gave a solid basis to his theories. The actual state of our present knowledge may be summed up as follows:

In the human groups of our older civilizations, at any rate, the individual encounters tubercle bacilli during childhood and, on account of the receptive tendency of the race, man harbors tuberculous infection at an early age. We shall soon see what happens subsequently. We may say at once that, when an adult becomes or, rather, appears to become tuberculous, the disease is really either the outcome of a fresh infection, of a new contagion from outside which becomes engrafted upon the original infection of early life; or it is the manifestation of a revival, a renewal of the old infection. In the first instance we are dealing with what I have already called an *exogenous* reinfection; in the second, with an *endogenous* reinfection.

From all the research work which has been carried out on this point (among others my own work in collaboration with Mr. Denoyelle), it would appear that under such social conditions as prevail in all countries

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of our civilization, an endogenous reinfection is far more frequently the cause of manifest tuberculosis among adults than is an exogenous reinfection: in any case tuberculosis among adults is always the result of a reinfection.

There are, however, a few exceptions to this rule which must be mentioned. It may happen that human individuals reach adult age without having encountered tubercle bacilli, either because they belong to races that do not live under social conditions of conglomeration, as is the case with the black races of Africa or other peoples or nations whose habits of life differ entirely from our own, or because, in our countries, they have until adult age lived away from towns, in peculiar conditions of isolation. These individuals, although they have reached maturity, may then become exposed to a first bacillary assault; as a matter of fact, they react in a way which recalls the symptoms usually observed among children and not among adults.

Such facts, however, are of a very peculiar nature, and, far from detracting from the original rule, they corroborate it in the light of the etiological factors which govern their genesis. Let us again insist upon this rule: in our countries with an ancient civilization involving human conglomerations, tuberculosis starts in childhood; when the child is not killed by it the disease declines more or less rapidly after passing through a series of clinical and anatomical stages, and leaves, as the only token of its existence, the phenomenon which reveals the presence of tubercle bacilli, that is, the tuberculin reactions.

The cutireaction of Pirquet and Mantoux's intracutaneous reaction represent the simplest, most reliable and most innocuous tests for detecting this phenomenon. Authors are agreed that in urban communities healthy adults show a positive cutireaction in 90 to 97 per cent of the population, an observation which has aided in strengthening the ideas we have just summarized and is a sound proof that the onset of tuberculosis takes place during childhood, for the almost universal incidence of infection is almost reached by the time of late adolescence.

II

The first question to arise is: Under what conditions does tuberculous infection take place, and why does it occur during childhood?

The last point is easily answered: the human race is, natively, markedly susceptible to the tubercle bacillus; as soon as a human being comes

in contact with an adequate number of virulent bacilli he becomes infected. The factors which determine this infection are thus involved in those of the first encounter between man and the bacillus.

A distinction must be made in this respect between two periods of childhood. During the first year of life the human infant, incapable of moving of its own accord, is confined within a very narrow space; its relationships, limited to the family circle, are few and restricted; in fact, when an inquiry is made into the etiology of a tuberculous infant one always finds a family or domestic origin of the disease.

After the second, and chiefly after the third year of life, the circles into which the child moves, as well as the number of individuals with whom it becomes connected increase in direct ratio to its age. It comes into touch with the ground, the street, other children, an increasing number of people and, finally, the school. In proportion as the child progresses in life and as its surroundings become more varied, inquiries as to etiological factors become increasingly unsuccessful. In many cases one detects tuberculosis in the family; in many other cases, however, the origin of the disease is either found elsewhere or baffles all investigations.

A more detailed inquiry into the sources of infection will strengthen and enlighten this fundamental distinction.

In 1923, I compiled with Mr. Robert Debré etiological statistics concerning 124 tuberculous infants. In 95 cases the mother was found to be tuberculous (the father was tuberculous as well in 20 cases); in 20 cases the father alone; in 3 cases more distant relatives, living under the same roof as the infant; in 6 cases, the servants or the nurse. All the records obtained since that period confirm this statement, and bring fresh arguments in favor of the notorious and constant existence of tuberculous contacts around an infected infant, the mother being the contagious agent in a considerable number of cases.

Isn't the fact that tuberculosis in the infant can so often be traced back to the mother an argument in favor of the heredity of the disease? It seems all the more urgent that this question should be investigated, inasmuch as new light has been shed over it by sensational research work. A little while ago most authors were agreed in rejecting this explanation. Opinions were practically unanimous in denying the existence of any cell-heredity (whether ovular or spermatic) of tubercle bacilli, and in admitting that transplacental heredity played only a very insignificant part. In fact, it was acknowledged, on the strength of a

few authentic records, that it was possible for tubercle bacilli to pass through the placenta and to give rise to lesions of congenital tuberculosis, but the number of these cases was so small that it was rightly considered that they could be neglected for practical purposes and that tuberculosis in an infant could be attributed solely to postnatal contagion through the mother or any other person.

Within recent years the theory of the heredity of tuberculosis has been rejuvenated in the light of new facts which must be summed up here. A few authorities (Bezançon and Philibert, Calmette and Valtis, Arloing and Dufourt, Durand) have recognized the fact, already put forward by Fontès (of Rio de Janeiro) and Vaudremer, that tubercle bacilli are endowed with pleomorphism, and that they can be transmuted into peculiar forms, capable of passing through the most minute filters, and of giving rise, when inoculated into guinea pigs, to normal acid-fast bacilli. Calmette and Valtis on the one hand, and Arloing and Dufourt on the other, have recorded the fact that in pregnant guinea pigs filterable forms of tubercle bacilli might pass through the placenta. In one human case Arloing and Dufourt claim that this phenomenon has occurred, but their demonstration is not quite convincing. However, Calmette seems to agree that the transplacental passage of these elements plays a not unimportant part.

In fact, clinical experience teaches that a number of infants born of tuberculous mothers die within the first three months of life, chiefly during the first month, without any tangible symptoms or lesions to account for the cause of death. These "unexplained deaths" have been investigated along very interesting lines by my pupil, Marcel Lelong, and my friend and colleague, Professor Couvelaire. If we consider, at one and the same time, unexplained deaths among infants born of tuberculous mothers and the experimental phenomenon of the transplacental passage of filterable forms of tubercle bacilli, we need only go one step further to attribute the deaths to this phenomenon. Calmette does not hesitate to do this, and ascribes a "high toxicity" to these elements. However, it has not yet been proved that these elements possess any peculiar noxiousness, nor that they are regularly detected in infants who have died under the conditions already mentioned.

As regards these purely hypothetical assumptions, one must insist on the following experimental facts which clearly contradict them: The first is the fact that one always finds a negative cutireaction in the infant, born of a tuberculous mother, who has been separated from its

mother immediately after birth. It may be objected to this that the filterable forms of tubercle bacilli do not give rise to tuberculin reactions; the question must be further elucidated, since this has not been done so far. The second fact is more convincing: children separated from their tuberculous mothers never become tuberculous. It may be objected that filterable forms are only capable of causing early, unexplained death and cannot give rise to true tuberculosis, but this would strangely restrict their sphere of action. A similar answer might be made to our third argument, namely, that, in cases in which infants have become infected not by their mother but by their father or any other tuberculous person, these cases are quite analogous to those in which the disease is of maternal origin; yet transplacental heredity is here out of the question.

We can deduce from these data that only unexplained deaths can be attributed to such heredity. As no evidence of this has yet been forthcoming we shall mention another objection which seems decisive, that is, the number of unexplained deaths in maternity clinics declines with the improvement in the living conditions of infants separated from their mothers at birth. Couvelaire, who noted this fact, has been able, thanks to efficacious measures, to bring down from 38 to 13 per cent the proportion of unexplained deaths.

The conclusion we may draw from the above consideration is that, until further evidence to the contrary has been brought forward, an heredity *of infection* must still be regarded as playing quite a negligible part in the etiology of tuberculosis, and that contagion is responsible for tuberculosis in the infant; maternal contagion in the majority of cases; contagion through other people, with whom the infant comes in contact, in exceptional instances.

We shall not waste much time on the part played in the case of maternal contagion by the passage of tubercle bacilli in breast-milk. This factor is negligible: the number of bacilli in the milk, in the majority of cases, is not large enough to infect the child. Moreover, contagion through the mother is observed as frequently among bottle-fed as among breast-fed infants (the latter being quite the minority in France). On the other hand, I have been able to ascertain the fact that, thanks to precautionary measures which aim at abolishing the projection of particles of sputum from the mother on to the infant at the time of feeding, tuberculous mothers may give the breast to their child without infecting it; in fact, it is the intimacy of contact involved in breast-feeding which makes the latter dangerous for the infant.

As regards children who are not exposed to maternal contagion, can artificial milk be incriminated? Personally, I do not think so for the following reasons: The bovine bacillus usually contained in cow's milk is comparatively innocuous to man, as confirmed by Koch. It is true that animal milk may become accidentally infected with the human bacillus. However, in France at any rate, most children are fed with sterilized or boiled milk, the risks of infection being in this way avoided. Moreover, in Japan, where until recently children were exclusively breast-fed, infantile tuberculosis was at least as widespread as in other countries where artificial feeding is practised.

Let us also mention a fundamental and striking fact: *in every case in which an infant born of a healthy mother has become tuberculous, a careful inquiry reveals a tuberculous contact.*

It is indeed contagion which gives rise to tuberculosis, and the contact which gives rise to contagion.

The mechanism of the infecting action of the contact is well-known: the sprinkling of the baby with Flügge's particles of mouth-spray, which carry tubercle bacilli into the infant's pharynx; thence their spread throughout the body.

It is not surprising under the circumstances that nursing the infant should be the most active and obvious means of infecting it: the tuberculous person who looks after the child represents the chief danger, and the risk increases directly with the assiduity and intimacy of the nursing.

The best evidence of the part played by contact in the onset of tuberculosis lies in the close and constant relationship between the conditions of contact and the consequences of contagion.

With Debré and Paraf I have been able to verify this at the *crêche* of the Laennec Hospital under the experimental conditions realized there. This *crêche* admits infants whose fathers or mothers are tuberculous. From the moment the child is admitted absolute separation is insisted upon between the child on the one hand and the father and mother on the other, the latter being isolated in distant wards and having no intercourse whatever with the child. Details as to the organization of this infant-welfare centre for the prevention of tuberculosis have already been described many times by myself or my collaborators. The complete break in the contact enables one to watch the consequences of the previous contact. Briefly, we have been led to the conclusion, as a result of these observations, that the conditions in which the contact had

occurred before it was broken have a direct and constant relationship with its consequences; according to the conditions of contact the child has or has not escaped infection and, in the latter case, the gravity of the disease is still dependent upon these same conditions.

The variations of this relationship follow the fundamental law, confirmed both by experimental inoculations into guinea pigs and by clinical infection in the infant, according to which a tuberculous infection is directly related in its genesis and evolution to the number of infecting bacilli.

This law explains the following experimental facts which are the outcome as well as the basis of its manifestations. They may be classified under four headings which may be summed up as rules:

1: The consequences of the contact are related to the abundance of the bacillary source. A phthisical patient whose sputum is swarming with innumerable bacilli is more likely to infect his child than an individual with only a few bacilli in his sputum, a tuberculous patient who expectorates bacilli in small numbers and intermittently.

2: The intimacy of the contact plays an equally important part; for this reason a tuberculous mother who is constantly living with her child and looking after him is more dangerous than a father whose relationship is neither so close nor so frequent. I have seen a very suggestive case in this respect. A tuberculous mother had twin children, seven months old when they came to my notice. The mother had a distinct preference for one of these children, looking almost exclusively after it while she neglected the other in whom she did not appear to take any interest; the first child alone gave a positive tuberculin reaction, the other a negative reaction.

The intimacy of the contact is the most important point to be considered in appreciating the influence of housing conditions in the etiology of the disease.

3: The duration of contact is the third factor which must be taken into account. In fact tuberculous infection does not occur as the result of a single, fleeting and rapid contact like most other infectious diseases due to human contagion. When the contact is brief no contagion occurs; the more lasting the contact the greater the risks. Only very exceptionally does it happen that an infant escapes being infected after a contact of over six months, and in such a case its good fortune must be explained by the happy interference of the other factors. It is equally exceptional that a contact which has lasted less than a month should succeed in bringing about infection. However, this rule is not absolute. I might mention the case of a child who had been preserved by separating it from the mother at birth; when the child was

twenty-three and a half months old, the mother, under an emotional impulse, took it away, and kept it with her for fourteen days, kissing it repeatedly and not leaving it for a moment. When the child had been again separated its cutireaction became positive twenty-five days later.

4: The last important factor concerns the age of the child. This factor acts oppositely to the three preceding factors. In the days immediately following birth a very short contact, when it is intimate, may be sufficient. I have published the case of a child who three times in the early days of life had an intimate contact, lasting five minutes, with its tuberculous mother; five weeks later a positive cutireaction was observed. I have seen another case, a child who, by mistake, remained in contact with its tuberculous mother during the first forty-eight hours of life; three months later the child died of meningitis. A number of similar facts have been recorded in the literature (Unverricht, Schloss, Petschark).

Briefly, the contact, all other things being equal, is dangerous in proportion to the infancy of the child. The further from birth, the more prolonged, intimate and rich in bacilli must the contact be in order to produce contagion. All these facts clearly illustrate the bond which unites the conditions and consequences of the contact as well as the mechanism of contagion. The latter may be summed up under the two following propositions:

1: Contagion is the outcome of à series of repeated inoculations, with, in certain instances, the very rare exception of a single, massive inoculation.

2: The consequences of contagion depend upon the numbers of inoculated bacilli. This experimental fact, well-known in laboratories, has been confirmed in the most striking manner by our observations among infants.

Among older children, as has been said, these circumstances are not so easily detected; yet at that age occult infections derived from sources containing but few bacilli play an increasingly important part. Of 30 cases between 3 and 15 years of age, whom I kept under observation in collaboration with M. Vitry, and whose cutireaction, previously negative, had become positive, a thorough inquiry yielded results in four cases only, the source of contagion being in the family; in the other 26 cases the inquiry was negative.

With Robert Debré, I have tried to ascertain how frequently, at what time, and under what conditions the appearance of a positive reaction takes place in children preserved from family contagion and brought up in the country and protected from any known source of infection.

We were able to undertake this inquiry thanks to the *Oeuvre du Placement Familial des Tout-Petits*, created for the preservation of infants against tuberculosis.

Of 300 children placed in these conditions, free from tuberculosis, we have seen, at distant dates from their separation, a positive cutireaction appear in 5 cases. We have excluded from these statistics all those in whom the delay of appearance of the cutireaction seemed too short to enable us to state positively that the previous family contact, which had been interrupted, could not be incriminated.

What hypothesis can be offered in order to explain the appearance of a cutireaction in these 5 children? A first hypothesis, which would attribute to a tuberculin sensitization the late appearance of the reaction must be excluded, as the reactions were few and far between.

The conjecture, that a suspicious contact might have infected the child, holds good in only one of our five cases: the inquiry revealed the fact that the peasant to whom the child had been entrusted had been admitted to a sanatorium 12 years previously and had suffered from arthritis of the knee. In the 4 other cases nothing suspicious was disclosed.

As regards these cases we are faced with three hypotheses: (1) either the late appearance of a positive cutireaction was due to an abnormal extension of the incubation period, the ante-allergic period of the disease which will soon be referred to; or (2) it is a late manifestation of a transplacental heredity; or again (3) it is the expression of a recent, but occult infection, the kind of infection which overtakes the immense majority of human beings before they reach adult age.

We shall now see how these hypotheses apply to these four children. One of them had been in contact with its tuberculous mother and, strictly speaking, the two first hypotheses might be put forward; in this case, however, the incubation would have lasted between six months and a year. It must be admitted that both the hypotheses of a late heredity and of an indefinitely prolonged ante-allergic period are not very probable, and that they do not afford a very clear explanation of the facts,—less so certainly than the hypothesis of an occult infection.

The three remaining cases are even more in favor of the latter probability. The cases concerned are those of three children, separated from birth and protected from any contact with their tuberculous parent; one is therefore entitled to rule out altogether the hypothesis of a prolonged ante-allergic period. In one of these children the cutireaction

became positive one year, in the second two years and 8 months, and in the third three years and a half after their separation. As regards the two children whose mothers were tuberculous one might, strictly speaking, assume a latent transplacental heredity of strangely abnormal duration. In the third case, however, this assumption cannot be entertained, as the tuberculous parent was the father. In this case one interpretation only is possible, namely, that of an occult infection.

This interpretation is most likely the one that applies best to the five cases, at any rate to the last four cases. One is entitled to assume that, if there is such a thing as a latent heredity with late manifestations, it would be detected more often than is actually the case in children placed under such special conditions of observation. On the contrary, it will be easily understood that occult infections should be relatively rare among them, as these children live in the country and are only kept under observation until the age of four.

We think that these facts, observed under circumstances approaching as nearly as possible experimental conditions, deserve to be recorded and remembered.

III

We have just examined the conditions under which tuberculous infection occurs, these conditions explaining likewise why it occurs during childhood. We shall now inquire into the early manifestations of this infection and their clinical expression.

To begin with, one must insist on the striking contrast between the threatening gravity of an invasion of the body by tubercle bacilli and the modest appearances assumed by such an invasion at this early stage, although the whole future of the individual is at stake.

In the immense majority of cases the first tuberculous lesion is a small nodule situated in the pulmonary parenchyma, most often in the right middle or lower lobe; simultaneously, one observes a caseous lymph node in the corresponding lymphatic group. This double alteration, whose symbiosis has been well illustrated by Parrot and later by Küss, constitutes the primitive glandular-pulmonary lesion. We shall not go into the question here as to whether this lesion really represents the entrance lesion of the bacilli, or whether, as Calmette believes, it is secondary to their introduction through the bowel; the presence of mesenteric lymph nodes characteristic of the latter process is indeed, sometimes but not always, observed at the necropsy, together with tracheobronchial adenopathy.

We shall be content to mention the constant presence of this glandular-pulmonary lesion at the origin of every first tuberculous infection.

For a better understanding of our account it will be interesting to describe the main features of the evolution of this anatomical starting-point, pregnant with pathological possibilities. Several eventualities may occur. In the first instance this primitive lesion may assume a deadly course from the start. This may occur in one continuous, or in several successive phases. The pulmonary nodule develops into a large centre of consolidation where the bacillus gives rise throughout the organ to new foci, which become more or less fused together; cavity formation may take place in the course of a relatively slow evolution or, on the other hand, a miliary tuberculosis may bring on an acute crisis. Such are the varieties of fatal tuberculosis in the infant, the only form acknowledged until recently.

In another group the primitive lesion becomes arrested; after a variable period of activity it becomes more or less latent, and transformed into scar-tissue. However, during that time a hidden process is evolving, characteristic of what one might call the secondary period of the disease. This occult process begins in the primitive lesion and scatters bacilli throughout the intrapulmonary lymphatics, giving rise to a lymphatic and connective-tissue reaction which becomes gradually sclerosed. These centres of sclerosis around the hilum of the lung, tokens of the old arrested tuberculosis, are found in almost all adults whose infection is revealed only by a positive cutireaction.

In the course of this secondary period which covers the long and insidious anatomical process, unexpected and sensational episodes may occur. There may be either a local flaring up of the original focus, which gives rise to the clinical signs and symptoms of a tracheobronchial adenopathy; or a migration of bacilli into the blood or lymph-vessels and the appearance of the various forms of localized tuberculosis (of the bones, joints, peritoneum, meninges, etc.). These are the usual varieties of tuberculosis during the second period of childhood.

Finally, whether the secondary stage took place quietly or was marked by conspicuous incidents, the adult, under influences with which we are not now concerned, may witness a revival of the activity of the bacilli enclosed within his old foci, these bacilli giving rise to fresh manifestations, which are characteristic of adult tuberculosis, and represent a truly tertiary stage of the disease. A study of the tertiary or of the secondary stage of tuberculous infection, or even of the numerous modes

of evolution of the primary stage, does not come within the scope of this account, which is merely concerned with the onset of tuberculosis; nevertheless, this rapid synthesis has enabled us to draw the outlines of our subject, which is in this way circumscribed to the actual invasion of the body by the bacillus.

This invasion includes two stages. In the first, the bacillus has become introduced, but this is not yet revealed by any outward sign. This constitutes a true incubation period of the disease, and has been called by Debré and Jacquet the *ante-allergic* period. The second stage starts with the appearance of the first revealing sign of the presence of the bacillus, that is, the tuberculin reactions, chiefly the cutireaction. We shall study these two stages in turn.

The ante-allergic period can be demonstrated, defined and measured by the time between the cessation of the infecting contact and the appearance of a cutireaction. To ascertain the length of this delay, the child must be separated from the agent of contagion and a series of cutireactions applied every 5 or 6 days until a positive reaction is obtained. The duration of the ante-allergic period is very variable: lasting from a few days to a few months, the average is from three to five weeks. We cannot understand how Epstein and Berthold have pretended that in man the ante-allergic period lasts constantly between three and seven weeks, whatever the age of the individual. They know as well as we do that, in the animal, the duration is variable and depends upon the infecting dose. This experimental fact is beyond doubt; it has been established by Debré and his collaborators in my laboratory; moreover, it can be verified wth striking clearness among infants. We have seen that among them the duration of the ante-allergic period is inversely proportional to the abundance of the infecting source, and exceptions to this rule are very rare. It leads moreover to another rule, which affords a practical and invaluable guide, namely, that the duration of the ante-allergic period is inversely proportional to the severity of the infection. The shorter this period, the greater are the risks of a fatal evolution of the disease; the longer the period, the more likely are the chances of the infection becoming arrested.

From a clinical standpoint this is the most important fact to be remembered in connection with the ante-allergic period, a period characterized, in fact, by its absolute latency, for not a single symptom betrays it.

It ends with the appearance of a cutireaction, the first manifestation

of tuberculosis, a manifestation however which has been provoked by external interference.

In an animal inoculated with tubercle bacilli, the anatomical tuberculous reactions appear at the same time as the first organized tuberculous lesions may be recognized. This classical fact, based on the experiments of Allen Krause and Robert Debré, has recently been challenged by Boquet and Nègre; but the experiments of the latter authors do not appear convincing to us, and, until further evidence to the contrary, we consider as a fact beyond doubt the simultaneous production in the animal of tuberculous lesions and capacity for tuberculin reactions; at the most, one may consider that this law has not yet been proved to apply to modified forms of the bacillus (for instance, *BCG* bacilli or filterable forms).

It is indubitable that the facts concerning first tuberculous infections observed in infants tend to show that a positive cutireaction is the first sign that reveals it. Often doubtful at first, the reaction becomes evident upon repeating the test. However, the degree of reaction has no prognostic value whatever in the infant.

Does the onset of the disease, detected by this method, show any spontaneous clinical manifestations? A great many authors deny it. Hess did not observe any such manifestations in the course of a kind of home-epidemic involving 7 children; neither did Schloss, although the temperature charts he has published show febrile attacks which he was unable to interpret in the absence of a cutireaction. Kleinschmidt, Hamburger, Gietl, and Arnould insist on the same absence of symptoms.

On the other hand, H. Koch, Ribadeau-Dumas, and Länger have mentioned such symptoms. Finally, Robert Debré and Laplane have published a very good report on the subject, to which we shall make but very few alterations, since the arguments have been borrowed from the same source as our own, the *crêche* of the *Hôpital Laennec;* all the facts which have since come to our notice have merely confirmed the accuracy of their conclusions.

Indeed the initial symptoms of tuberculosis, or rather of the first tuberculosis crisis, are generally so unobtrusive that they have long remained unnoticed. One merely observes, at the time when the cutireaction (negative so far) becomes positive, a slight rise of temperature lasting between one and several days; a small loss of weight, the latter perhaps remaining simply stationary; sometimes the stools may be more

frequent, undigested or even greenish,—that is all; in two to five days everything is again in order.

The strange contrast between the redoubtable future of this morbid aggression and its initial unobtrusive appearance deserves to be pointed out.

Very rarely a few local symptoms become added to this clinical picture. Sometimes the child may have a slight cough and, in a few instances, physical signs may be detected in the thorax, in the interpretation of which the greatest caution must be observed. In some cases the stethoscope brings out bronchial breathing or a few fine râles in one of the lungs. Of course, one must not expect to find here the classical signs of tracheobronchial adenopathy, the value of which, as a matter of fact, is open to criticisms which we have specified elsewhere.

Similarly, the interpretation of radiological findings must be very guarded. To begin with, we may mention that a *radiosdopic* examination is quite inadequate in these cases, *radiography* being imperative. In infants special precautions are necessary, since it is indispensable to take into account technical factors, chief among which is the patient's position. Such differences in position involve differences in the pictures, which may give rise to serious mistakes; among other things, the place occupied by the thymo-cardiac shadow varies considerably, according to the position of the child, and this may lead to confusion.

With this important reservation, three kinds of shadows may attract notice. *First*, small spots around and above the cardiac region may be mistaken for lymph nodes; they are, in fact, normal shadows, probably of a vascular nature, as has been demonstrated by Chaperon, Delherm and others. *Second*, a spot may be seen right in the pulmonary area; in this case, we are dealing with the primary nodule; this eventuality is, however, rather exceptional. *Finally*, a large area of the lung may be obscured by an extensive shadow with an indistinct outline; this is the only radiographic appearance which cannot give rise to controversy, for, as we shall see, its subsequent evolution confirms the pathological nature of these shadows.

On the whole, the radiological study of the first tuberculous outbreak, while it must be based on a thorough knowledge of the difficulties involved, may occasionally afford important information; however, its variable character must not be lost sight of.

These then are the only clinical signs of the onset of human tuberculosis. They may be quite absent; they are usually trifling and tran-

sient; they may be more obvious, and the disease may even evolve toward a fatal ending, or toward cure.

I shall recall, as an example, the case of this child whom I have already mentioned, who had been separated and preserved, and who was then taken away by the mother at the age of 23 months and infected after a 14-days' contact with her. At the end of an ante-allergic period, which lasted 25 days, during which the child preserved a flourishing appearance and increased in size, the following symptoms were suddenly observed while the cutaneous reaction had become positive. The child looked ill and had lost its spirits; there was some diarrhoea; its temperature rose to 38° and nearly reached 39°C.; there was an abrupt loss of weight, the latter coming down within a month from 11,400 to 10,500 gm., while, at the same time, the stethoscopic signs of a pulmonary focus had appeared on the right side while a large shadow could be seen in the middle lobe of the right lung. After an acute evolution, which lasted a month and during which the child went progressively downhill, all the pathological phenomena disappeared. The weight returned to its previous level, the temperature again became normal, the child recovered its spirits and fine appearance, and the physical signs, whether radiological or stethoscopic, disappeared altogether.

This is a typical case of an obvious first tuberculous outbreak. Such cases are exceptional, when compared to those with unobtrusive and fleeting symptoms, hardly noticeable at the time. One may come across a typical symptom. We have seen a case, in which the first attack, which appeared after an ante-allergic period of 40 days in an infant exposed to a maternal contact for two and a half months after birth, was characterized by a rise of temperature, which did not interrupt the progressive gain in weight. There was a large shadow accompanied by stethoscopic signs. Marked anaemia was the most striking symptom, the child becoming very pale, with a blood count of 3,160,000 red cells and 8,000 leucocytes, and without any abnormal shapes. The disease lasted altogether two months and everything became normal again.

These statements apply to children placed under our special conditions of observation, that is to say, children taken away from the contagious agent. The interruption of the contact enables one to detect the early onset of tuberculosis, disentangled from the series of progressive symptoms which characterize the disease in children constantly exposed to infection and stricken with those forms of tuberculosis which are nearly always fatal, and which have been described in classical literature.

In some instances, however, a different clinical syndrome is observed. I am referring to those forms of the disease, which evolve toward cure and which have already been described by J. Paraf and myself. The cases concerned are usually children who, after an ante-allergic period lasting one to three weeks, get an acute attack of bronchopneumonia, the tuberculous nature of which is revealed by the simultaneous appearance of a cutireaction and sometimes by the presence of tubercle bacilli in the stools. This bronchopneumonia is usually cured within a month, in spite of the fears which may have been raised by the threatening general condition as well as the marked pulmonary signs of the little patient.

Finally, in other cases, the evolution of the disease is not arrested. With a bronchopneumonia syndrome or with signs of acute miliary tuberculosis, the first tuberculous attack leads straight on to death.

We might now bring to an end our consideration of the onset of human tuberculosis, inasmuch as we have made a very thorough examination of the various forms which the first outbreak may assume.

We believe, however, that it may prove interesting to describe briefly what becomes of children who have not succumbed to this first attack, as is generally the case when they have been taken away from the contagious agent.

Three eventualities may occur. In the first instance there are children who, after the latent or obvious onset of the infection, assume their normal appearance, and then, a month or so later, have one or several acute crises, which may be either benign or fatal. Often among children, who succumb to one of the fatal forms of infantile tuberculosis, either acute miliary tuberculosis or the afebrile, cachetic, chronic form of Marfan, one might have detected the previous initial outbreak if they had been placed under suitable conditions of observation: this happened in two of our cases. In the second eventuality the first outbreak has been completely arrested, and the child has reached the secondary stage of the disease to which I have already referred. Yet a slow, insidious process is going on in the depths of the organism; one that may be betrayed by slight alterations of the general health, the most apparent being minor symptoms of rickets. We are dealing here with small children with a positive cutireaction, defective growth subject to ups and downs, a pale complexion, and a few bony deformities; usually this delayed growth becomes rectified and, after a certain length of time, the child is again normal.

In the third and last eventuality tuberculosis remains altogether

latent. If the onset has also been insidious we are dealing with one of those cases of the outbreak of tuberculosis which are betrayed only by a positive cutireaction, and which never give rise to any symptoms.

I have thus far dealt only with the onset of tuberculosis in the infant. When an older child is first infected is there any difference in the symptoms observed? The answer is a negative. Indeed, in the infant as in the older child or even the adult, it is not the age of the patient which governs the morphology of the disease, but the duration and mass of the infection, and, above all, the relationship between this infection and the specific, humoral conditions of the body. If the first infection occurs in an older child, or in adult life, it takes on one of those specific appearances which are identical with those observed in the infant.

In fact, with Vitry among older children at the *Ecole de Puériculture*, or with Debré among children from the *Familial Placement Centre*, who had yielded ultimately a positive cutireaction, I have not observed any symptoms accompanying this cutireaction. The onset was quite insidious; in the statistics which I have amassed with M. Vitry this happened in 11 out of 30 cases.

Most frequently, however, the appearance of a positive reaction is seen to coincide with a few slight symptoms, which can only be detected as the result of careful observation and inquiry. Such symptoms are identical with those which we have already described, such as a malaise lasting a few days, characterized by slight intestinal trouble, a loss of weight, a transient rise of temperature, and sometimes a few local stethoscopic or radiological signs.

Such is the onset of tuberculosis in the older child. The usual pathological forms of tuberculosis in the second period of childhood belong to two other classes of phenomena: either the primary lymph-node-pulmonary lesion remains active and gives rise to manifestations of tracheobronchial adenopathy, the primary infection having in some way become extended into the second period of childhood; or, after the primary lesion has been arrested, tuberculosis enters upon its secondary stage. In the latter eventuality it may then give rise to a flaring up of the pulmonary focus, as happens in the adult, when one might speak of a premature tertiary stage; or it may also, thanks to a migration of bacilli into the blood or lymph, give rise to the usual manifestations of tuberculosis of the various organs,—the viscera, serous membranes, bones, joints, etc.

IV

From the foregoing considerations it will have been seen how widely our knowledge of the onset of tuberculosis in man has become altered as the result of experimental research work and clinical investigations.

It is the child who, under the ordinary social conditions prevailing to-day, bears the weight and brunt of it all. According to its age, according to the circumstances in which it comes in contact with the bacillus, these circumstances being determined by the abundance and incidental conditions of the contagion, according also to the measures taken to meet the bacillary aggression, the course of which is either interrupted or allowed to progress, the child reacts in one of the various ways we have analyzed, from the complete absence of any spontaneous manifestations to the most severe and fatal forms of the disease.

In the ordinary course of events, however, the onset of the infection is as insidious as the disease may be ultimately baneful; yet there is a sign, or rather a test, which will always help to detect it,—the tuberculin reaction.

This explains why the initial manifestations of tuberculosis have been so long disregarded, as well also as why the disease is always so difficult to detect. Only through a thorough knowledge of the difficulties involved and under special conditions of observation, will the physician be able to make a precise and accurate diagnosis. To this end a knowledge of the use of tuberculin reactions is even more helpful than is semiotic analysis, including radiography.

One must not lose sight of the fact that the dispensary is the most useful agency for the detection of the disease. It is through the dispensary that one is able to trace out children belonging to contaminated homes, and to find to what extent they have been infected.

However, in order that such an inquiry may yield results, one must not be content with a single cutireaction. If the latter is negative it must be repeated again and again, repeated apart from any fresh infection. It is therefore necessary to separate the child from the agent of contagion; hence the need of centres of observation such as the centre I have created at the *crêche* of the *Hôpital Laennec.*

Such a measure is as helpful in the treatment of the disease as in its diagnosis. In fact, there is no really adequate therapeutic method against the first tuberculous infection; while in the case of progressive lesions artificial pneumothorax, which has been attempted several times, meets with insuperable difficulties and gives no result. Prophylaxis is the only therapeutic method at our disposal; it consists in putting an

end to repeated inoculations by the contagious agent through the separation of the child.

If the child can be separated before it has been exposed to any tuberculous contact, the absolute prevention of the disease will be realized; our experience of over six years enables us to justify this statement by unanswerable arguments based on facts. Yet, even when the contact could not be avoided, even when contagion has already occurred, there is still an immense benefit to be derived from separation, as, by its means, an end is put to the series of infections resulting from the contact. The consequences of contagion are in this way limited, so that a process which might otherwise have been fatal becomes transformed into a benign form of the disease. Thanks to this method, the prognosis of infantile tuberculosis, formerly invariably bad, has undergone a great transformation. The disease, not long ago unconquerable, has been reduced to its very earliest manifestations; and, while one has been able to identify its initial symptoms, one has succeeded in circumscribing the evil.

These same principles of separation immediately after birth (antenatal prophylaxis) or of separation after the contact has occurred (postnatal prophylaxis) have been applied to the organization we have created in Paris in collaboration with Madame Arnold Seligmann and Robert Debré.

Briefly, this organization consists, besides a *crêche* for the prevention of tuberculosis, and besides the connection between my dispensary and several provincial dispensaries and maternity clinics, of *Centres of Family Placement* in the country where infants, removed from contagion and previously kept under observation according to the rules we have established, are placed under special supervision.

This prophylactic organization is complex. If it works out in the extremely satisfactory manner we have often been able to demonstrate, it is thanks to the fact that it is backed by a very powerful and efficient hospital social service, for whose development in Paris we are indebted to our women friends from the United States.

Another prophylactic method will probably become added to ours, the specific prevention of tuberculosis by means of Calmette's vaccine. We are not concerned here with the details of this discovery, the practical application of which has given rise to great hopes. If time brings, as it no doubt will do, further proofs to confirm its practical value, this will in no way detract from the strength and the validity of the principle of separation which enables one to make the early diagnosis of a tuberculous outbreak and to save the lives of the children.

ERRORS AND DIFFICULTIES IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS[1]

FRIEDRICH vonMÜLLER[2]

The early diagnosis of incipient tuberculosis of the lungs is one of the most common problems with which the practitioner has to deal. The task is not only frequent, but also full of difficulties and of the greatest responsibility. The earlier the diagnosis can be made the surer we are that treatment will be able to produce full restoration of health. The physician is therefore inclined to establish this diagnosis upon the slightest symptoms: a trifling elevation of temperature, some loss of weight and strength arouses suspicion, and in such cases it is necessary to have a certain independence and critique *not* to find a little difference of percussion and auscultation at the apices; and even when no real difference between *both* sides can be found the doctor thinks that the percussion note at *both* apices is a trifle duller than it ought to be, and that *both* lungs may be affected. When a physician says that he has found dulness at both apices, I am inclined to think that he is a cautious man, who is under the prejudice that the patient must have a pulmonary affection; that he is not sure which of the two sides is affected and, if he says both sides, then at least he hits it on one side.

Are we not in certain cases prejudiced in our diagnosis before we begin to examine the patient, only because he gave us a history suspicious of tuberculosis? Very often further observation of the case or a good X-ray picture shows that our overrefined diagnosis was wrong, and in such a case the faulty diagnosis has done great harm to the patient. We have not only brought upon him and his family great sorrow and involved them in much expense of money and time, but the diagnosis of tuberculosis marks the patient with a stigma. It is difficult to wipe out this mark, which may hinder a marriage or prevent children; moreover, a long cure in a sanatorium spoils the man, makes him unfit for earnest work, and makes him for years a hypochondriac.

[1] Presented at a session on *The General Treatment of Tuberculosis*, before the Clinical Section of the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 6, 1926.

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I remember more than one case in which an abortion has been induced in a young woman on the diagnosis of tuberculosis made by well-known physicians. The operation turned out disastrously, and the postmortem did not reveal a trace of tuberculosis of the lungs.

Pfaundler has pointed out how often slight rises of temperature lead to the faulty diagnosis of tuberculosis in infants; and he goes so far as to say that swelling of the lymph nodes of the neck behind the sternocleidomastoid (the so called *Polymicroadenia* of infants) is not a sign of tuberculosis but of simple lymphatism. D'Espine attributes great importance to slight dulness in the interscapular region near the vertebral column as a sign of tuberculous swelling of the bronchial lymph nodes. But the bronchial lymph nodes are situated so deeply in the middle of the thoracic cavity that an increase in their size can never be detected by percussion. We were able to show that a focus of consolidation, and even a large tumor or aneurysm, can be discovered by percussion only when it is situated rather near the surface of the lungs and not deeper than 4 cm. below it.

The alleged dulness in the interscapular area is found in all normal individuals, and it is due to the thick muscular layer of the trapezius.

We must bear in mind that the diagnosis of a *primary focus* is never possible by percussion and auscultation. The size of such a primary infection is commonly not bigger than a pea, and it is more often localized in the middle and lower parts of the lungs than in the apex. The discovery of such a small focus by percussion and auscultation would not be easier than determining by the same methods which of two boxes of cotton wool contains a hidden pea.

To-day a good X-ray photograph is indispensable in every case because every tuberculous affection produces an infiltration and a swelling of the local lymph node. Therefore a tuberculous focus should not escape our eyes. Mistakes are possible only when the focus is behind the ribs or within the shadow of the vertebral column or the heart. A tuberculous focus of the lungs hardly ever heals without leaving a scar and we are therefore able to judge, even after many years, whether a tuberculous infection has been present or not. It is not exceptional to see cases in which a cure of tuberculosis had been called a most splendid result, while the X-ray shows that in fact there never had been a tuberculous infection at all.

If we follow the modern literature we feel inclined to say that the old methods of percussion and auscultation have lost their importance. I

think, on the contrary, that they have gained enormously in reliability since we have become able to control them by radiological findings. On the other hand, percussion and auscultation are indispensable in explaining the X-ray photograph; at least, the X-ray photograph has shown that an overrefined physical examination very often has led to error.

For many years I have tried, together with my assistants, Selling, Edens and Martini, to study the real physical nature of percussion and auscultatory phenomena, and to introduce the terminology of scientific physics instead of the old artistic one.

So I propose to designate the terms *loud* and *soft* as the expression of the amplitude; *high* and *low pitch* as the expression of the number of vibrations to the second; and *long* and *short*, the total duration of the percussion sound produced.

We were able to make correct tracings of the percussion sounds with the phonograph of Otto Frank, and I wish to show you the original photograms (these were displayed at the meeting).

We realized that the sound of a normal lung is very low, with an average of 108 vibrations to the second. The so called *relative dulness* of the thin edges of the borders of the lung give a higher pitch and a smaller amplitude wherever the thickness is less than 4 cm. The lungs of children give a higher pitch than those of adults. The sound of emphysematous distended lungs is lower than normal, and so is the sound of a large pneumothorax.

In case of a smaller *infiltration* the sound becomes first of higher pitch, and it loses its low fundamental vibrations. In fact, a small focus at one of the apices does not give a real dulness, that is, a smaller amplitude, but it betrays itself first by a higher pitch. As Auenbrugger says, *ubi sonus est altior ibi est morbus*. With the progression of the infiltration the sound becomes of smaller and smaller amplitude; and, in perfect pneumonic infiltration and even more so in pleuritic effusion, the ribs do not answer at all to the stroke of percussion because the consolidation of the lung or the pleuritic effusion checks their ability to vibrate.

The tympanitic sound of the bowels and of cavities of the lungs gives a far higher pitch than the normal lungs; it averages 300 per second, and metallic tinkle is the heighest we can conceive, being about 4,000. The foamy substance of the lung enforces its low sluggish vibrations upon the ribs. You may convince yourself very easily that the low normal sound of the thoracic wall responds to the proper tone of the lungs. Put your

hands on both sides of your own chest and sing the scale. You will feel no vibrations as long as you sing the upper parts of the scale. Below a certain point in the scale vibrations of the chest-wall become perceptible, and are strongest within the lowest notes of the bass voice.

You can convince yourself still better of the proper tone of the lung, if you put your ear on the chest-wall of your patient and let him speak. When you close your other ear you will not be able to understand what he says, because the higher tones of *ē*, *ā* and *ȧ* and most of the consonants are extinguished, and only the lowest tones remain as an indistinct murmur, like *ȯ* and *ü* and *mm*. In case of an infiltration *ē* and *ā* and *ȧ*, and especially the German *ch*, are heard perfectly well. This method is very reliable in discovering infiltrations in the lung when bronchial breath-sounds are not heard. Let the patient speak the German word *acht-und-sechzig* in a whispering voice as a proof of infiltration.

We found great difficulties in determining the physical nature of the *respiratory* sounds because these sounds are so soft, that we were not able to trace them with our best apparatus. We were only certain that bronchial breathing is identical with *Chi* from *ich* and has a rate of 1,000; *och* and *uch* are the sounds especially heard over cavities.

It is established that sounds like *Chi* show a very high frequency of 1,000 to 3,000, and this is the proper sound of the larger and the medium-sized bronchial tubes. The smaller bronchi give no perceptible sounds. In case of an infiltration the consolidated lung tissue produces no sounds. It is silent, but it acts as an excellent conductor for the sounds of the bronchial tubes, transmitting them to the chest-wall and to our ear.

The most difficult task was to establish the physical components of the vesicular breathing of the normal air-containing lung. We secured the aid of one of our best German musicians, the famous violinist Adolf Busch; and his trained ear found out that normal vesicular breathing corresponded to the low *A* with its 108 vibrations. That is the same tone which we found to be the normal percussion sound, and it seems that the lung responds like a resonator with its proper tone when it is struck by percussion or set into vibration by respiratory distention.

The normal air-containing lung is a very bad conductor of sound vibrations; therefore a small layer of normal lung tissue suppresses and deadens the high pitch of the bronchial tubes, and only the low vibrations of the lungs reach our ear. You can convince yourself of this phenomenon when you put your stethoscope first upon the tracheal tube and then over the sternum. The bronchial breathing of the trachea gradually

disappears, and is scarcely perceptible as soon as the thickness of lung tissue amounts to 2 to 4 cm.

The respiratory sound of the lung is an integration between the *low* fundamental vibrations produced by the expansion of the lung vesicles and the high pitch of the bronchial tubes. If we move the stethoscope from the trachea or the spinous process of the seventh cervical vertebra to the lateral and inferior parts of the thorax, the bronchial breathing gradually disappears, and in the lower posterior parts of the lungs the *Ch* is not heard at all. As soon as parts of the lung become infiltrated and more solid, the conduction of the high pitch improves and we hear mixed or sharper, that is, higher bronchovesicular breathing.

One would be inclined to think that the whole question of the percussion and auscultatory sounds is cleared up, since we have established the proper fundamental tone of the normal lung tissue and the bronchial tubes. But it is not so. The analysis of the speech-sounds by Helmholtz, Miller, Stumpf, Wagner and others has shown that the higher upper tones, the so called overtones, are most important for the character of the speech-sounds, and I think that the experienced ear of a skilled doctor often relies more on the overtones than on the fundamental tone. The study of the overtones in percussion and auscultation has not yet been achieved.

It is obvious that an examination by *physical* methods only tells us about *physical* conditions. The acoustic methods of percussion and auscultation and the optic examination by X-rays only allow us to distinguish normal air-containing lung from infiltrated and consolidated lung or perhaps an effusion of fluid or air in the thoracic cavity. But neither percussion nor auscultation nor X-ray permit us to distinguish the histological character of an infiltrative process, and I deny that we are able to distinguish sharply between exudative and proliferative processes.

I go so far as to say that the modern distinction between exudative and proliferative tuberculosis is only of anatomical but not of clinical importance for the doctor.

Of course the X-ray photograph allows us to determine whether a case shows single or multiple, smaller or larger nodules, or whether a more diffuse pneumonic affection has invaded a greater part of the lung. The X-ray allows us to distinguish a fresh focus, by its slighter shadows and its indistinct border-lines, from an old scar whose shadow shows a network of deep and distinct lines. We know that fibroid scar-tissue is the result

of a proliferative process, and we know that a fresh inflammatory infiltration usually represents the more exudative pneumonic character, but we cannot foresee whether an infiltration will turn to necrosis, caseation and destruction, or whether proliferative processes will prevail and lead to the formation of connective-tissue and scars. Even the presence and number of râles does not permit us to distinguish between exudative and proliferative foci, because not seldom in old fibroid cases the secretion is very abundant.

The question as to whether a process will extend rapidly and go on to a fatal issue, or else tend to recovery, depends, in great part, on the individual constitution, the power of resistance, and the degree of immunization. Unfortunately, we find no possibility of estimating the constitutional factor in the individual case. But it is not the constitutional factor alone upon which the fate of the patient depends. This does not decide whether the process will run the exudative or the proliferative way. For we see very often, in the postmortem room, that an old fibroid benign process of the upper lobes is combined with fresh exudative infiltrations of the lower lobes, and the accident of a profuse hemoptysis often leads to the sudden explosion of diffuse fresh exudative pneumonic infiltration.

Even an acute and rather extended pneumonic exudative infiltration does not necessarily turn to caseation and the formation of cavities, but not seldom it runs a benign course, diminishes in size and leaves a net-work of fine fibrous bands. The differentiation between exudative and proliferative tuberculosis is an expression of the momentary anatomical state, but not of the issue of the disease and the fate of the patient. When the physician wishes to make a prognosis, he places not so much importance upon the anatomical status as upon the clinical symptoms, the temperature, the pulse-rate, and especially the toxic symptoms, such as loss of appetite and strength. He distinguishes sharply between the open forms of tuberculous cavities and the closed ones, in which no bacilli can be found in the sputum. The cases of open tuberculosis constitute the real danger for the community, and the prevention of tuberculosis must begin with the exclusion of the bearers of bacilli, just as in typhoid fever, cholera, diphtheria and other infectious diseases.

THE MOST DEPENDABLE SYMPTOMS FOR MAKING A DIAGNOSIS OF EARLY CLINICAL PULMONARY TUBERCULOSIS[1]

F. M. POTTENGER

It is desirable to have the greatest possible degree of accuracy in the diagnosis of early active pulmonary tuberculosis. To fail to make the diagnosis, if an early active lesion is present, means to endanger the life of the patient; for the feeling of security resulting from a negative opinion often lulls the patient into a state of confidence accompanied by carelessness and indiscretion. On the other hand, the diagnosis of active tuberculosis, when the disease is not present, causes the individual unnecessary mental anxiety, forces him to follow a regimen which is unwarranted, causes serious disturbance in domestic and business relations, and causes him to meet a financial obligation which is unnecessary. While both mistakes are serious, yet even those who have had most experience in diagnosis will have to admit that now and then they are guilty of error. However, careful examination and time for studying the case before an opinion is given will eliminate the error in most instances.

There are several groups of cases in which error is likely to be made, such as (1) the asthenic, neurasthenic and psychasthenic group; (2) such endocrine disturbances as mild hyperthyroidism and hypothyroidism, hypergonadism and hypogonadism, and that condition of instability of the adrenal system which follows acute infections; and (3) the group of nontuberculous infections of the respiratory tract.

In order to understand the difficulty surrounding early diagnosis it is necessary to define what is meant by the term; but here we get into difficulty. What constitutes sufficient evidence upon which to base a diagnosis of early clinical tuberculosis must necessarily vary with individuals. I would define clinical tuberculosis as being that stage of the disease which produces sufficient harmful effects on the patient to interfere with the normal working of his body mechanism, and produce symptoms.

[1] Read at a meeting of the American Sanatorium Association, Washington, D. C., October 2, 1926.

Although tuberculosis may be present in the body of the individual for quite a time, it is not suspected until something goes wrong; until his physiological equilibrium is upset, and some function fails to be performed in its usual manner. Inasmuch as the physiological equilibrium of different individuals differs greatly in its stability, so must the amount of activity in a tuberculous process necessary to disturb function sufficiently to cause symptoms differ in different individuals. This point is not sufficiently appreciated in daily clinical work, and yet I am sure it is a fundamental fact in explaining the variability in the manifestations of disease processes. One patient will show symptoms on very slight stimulation, while another will withstand greater stimuli and still maintain physiological equilibrium. Every one then must be judged concretely, recognizing that while given stimuli have a tendency to produce such and such effects or symptoms, the effect produced will be more manifest than normal in those people whose physiological equilibrium is easily disturbed and less than normal in those whose equilibrium is extraordinarily stable.

For a number of years I have analyzed symptoms according to what I have chosen to term an *Etiological Classification* (1), as follows:

GROUP 1

Symptoms due to toxemia

Caused by harmful stimulation of	*Symptoms*
I. Nervous system in general	1. Malaise
II. Endocrine system in general	2. Lack of endurance
III. Body cells	3. Loss of strength
	4. Nervous instability
IV. Sympathetic nervous system	5. Diminished digestive activity
V. Sympathicotropic endocrines, particularly adrenals and thyroid	6. Increased metabolic rate
	7. Loss of weight
	8. Increased pulse rate
	9. Night sweats
	10. Temperature (partially)

GROUP 2

Symptoms due to reflex causes

Afferent nerves	*Symptoms*	*Efferent nerves*
Afferent through (vagus) parasympathetics	Hoarseness	Laryngeal nerves
	Laryngeal irritation	Superior laryngeal nerve
	Cough	Laryngeal, and nerves to all expiratory muscles with inhibition of nerves to inspiratory muscles
	Inhibition of heart	Motor fibres of cardiac vagus
	Increased muscle tonus, and glandular secretion in gastrointestinal canal	Motor fibres of gastric and intestinal parasympathetics
	Pylorospasm	Motor fibres of pyloric parasympathetics
	Flushing of face	Sensory fibres of trigeminus
	Spasm of sternocleidomastoideus and trapezius	Spinal accessorius
	Degeneration and deviation of tongue from median line	Hypoglossus
	Degeneration of facial muscles	Trigeminus and facialis
Inflammation of lung	Flushing of ear	Third sensory cervical
	Dilatation of pupil	Motor from Budge's Centre (lower cervical and upper dorsal)
	Spasm of muscles of shoulder girdle and diaphragm	Cervical motor nerves, IInd to VIIIth
	Lessened motion of chest-wall, partly due to muscle spasm as above	Cervical motor nerves, IInd to VIIIth
Afferent through sympathetics	Pain above 2nd rib and spine of scapula (superficial)	Cervical sensory nerves, particularly IIIrd, IVth and Vth
	Pain in muscles of shoulder girdle (deep pain)	Cervical sensory nerves, IInd to VIIIth
	Degeneration of skin and subcutaneous tissue above 2nd rib anteriorly and spine of scapula posteriorly	Cervical sensory nerves, IIIrd, IVth and Vth
	Degeneration of muscles of shoulder girdle	Cervical sensory and motor, IInd to VIIIth

GROUP 3

Symptoms and syndromes due to the process per se

Spitting of blood
Pleurisy (tuberculosis of the pleura)
Sputum (with or without tubercle bacilli)
Frequent and protracted colds (tuberculous bronchitis)

According to this classification the symptoms belong to three groups: (1) those due to the toxins and other factors which act generally, producing general or constitutional symptoms; (2) reflex symptoms, which may be expressed in any or all tissues supplied by neurons which mediate directly or indirectly in the afferent nerves from the lung; and (3) local symptoms due to the tuberculous process *per se.*

A careful analysis of these three groups of symptoms will make it plain that each group is produced in a different manner and, further, that every symptom of tuberculosis is due to one of these three causes.

Group 1. The toxic, general or constitutional group of symptoms is due to factors which act generally throughout the body. This fact must not be overlooked, even though the symptoms at times manifest themselves in certain organs or tissues more than in others. The probability is that the action is a triple one, and that it affects the entire neurocellular mechanism. It acts (1) through the nervous system and affects the tissues generally; (2) through certain endocrine glands (particularly the thyroid and adrenals), and through their internal secretion affects certain tissues and organs of the body; or (3) through the cells of the body direct, interfering with the normal physiological activity of their physicochemical phases.

Group 2: The reflex group is due to an inflammatory process in the lungs irritating the sensory nerve-endings of the sympathetics, and the vagus of the parasympathetics, thus causing impulses to travel centralward, to be mediated with efferent nerves and cause symptoms peripherally in the organs supplied by them. The number of nerves with which these afferent stimuli mediate are numerous and widespread, and the tissue and organs influenced comprise those in every part of the body. The more common symptoms of tuberculosis of a reflex nature, however, are found in the above table.

Group 3: The local group, or the group due to the tuberculous process *per se,* consists of those symptoms which are caused by the inflammatory process in the lung, which produces symptoms by its presence.

It is interesting that there is not a single symptom in group 1 that

alone would point to the lung or to tuberculosis as being its cause. The group belongs to any toxemia, to neurasthenic and psychasthenic states, and to numerous endocrine disturbances. In group 2, many of the symptoms appear in other organs, and unless considered in relationship to visceral reflex paths would point away from, rather than toward the lung; and, as far as nerve-paths are concerned, the stimulus causing the reflex in most instances could as well come from other organs as from the lungs. However, this is not true of those pulmonary viscerogenic reflexes which are expressed in the skeletal tissues. These are very important localizing symptoms. The motor, trophic and sensory reflexes from each organ, following Sherrington's law, express themselves most readily in definite skeletal areas. While the reflex spreads to neighboring and even distant structures at times, the usual areas for the reflexes are sufficiently definite and constant to make the pulmonary reflexes, which are expressed in the muscles, skin and subcutaneous tissues, of sufficient importance to be considered among diagnostic criteria of first rank in early pulmonary tuberculosis.

The motor reflex is an expression of active inflammation. It appears as soon as the nerve-endings are irritated, and does not disappear until activity has disappeared. The sensory reflex is not indicative of activity, but may be present both when the disease is active and when it has become quiescent or healed. The trophic reflex expresses chronicity, showing that the tissues have been subject to irritation for a long time. Since clinical tuberculosis is so often an extension or reactivation of a previous focus, the presence of the pulmonary trophic reflex gives a suggestion of the location of a previous lesion and indicates where activity may be expected.

Among the symptoms of group 3 we have the valuable localizing symptoms, hemoptysis, pleurisy and sputum, the latter particularly valuable when positive for tubercle bacilli. These symptoms are very significant, and call attention at once to the lungs as the cause. Frequent and protracted colds (chest colds) are very suggestive of tuberculosis, but alone are not sufficiently definite to be made the basis of a diagnosis. If they are accompanied by symptoms of groups 1 and 2, however, particularly the motor reflex from the lung, then they are definite.

The most important symptoms from the diagnostic standpoint in my experience are hemoptysis, pleurisy, sputum and the motor reflex from the lung. But more important than any one is the combination of symptoms of the various groups.

I have found that hemoptysis of a dram or so in quantity of bright red blood, which is not associated with an acute (and rarely a chronic) respiratory infection and does not come from bleeding gums or is not due to a heart lesion, can usually be considered as caused by a tuberculous process in the lung. But I feel surer if it is preceded or accompanied by some of the symptoms of group 1 and group 2, particularly a reflex spasm of the muscles on the affected side, which shows as a lagging or fixing of the side caused by shortening of the crus and central tendon of the diaphragm below and the scaleni and sternocleidomastoideus above; and as a spasm or an increased tension to the palpating finger in the muscles of the shoulder girdle, particularly the sternocleidomastoideus and trapezius; and, if the lower lobe is involved, the levator anguli scapulae and rhomboidei. The presence of nervous instability with malaise and loss of weight, with or without elevation of temperature, either preceding or following the blood-spitting, adds greatly to the weight of the evidence.

Pleurisy is also significant. Effusion which does not accompany pneumonia or the acute respiratory infections is strong evidence of a tuberculous etiology. The same may be said of dry pleurisy of the acute type, which causes sharp pain on breathing or coughing, and which is distinctly localized and accompanied by a spasm of the overlying portions of the intercostal muscles. This must be differentiated from the vague pains, which are so often present over the chest of patients who are at the time or who have in the past suffered from tuberculosis, mediastinitis or pleurisy, and which are to be looked upon as an expression of injured neurons, which respond with pain on a lesser stimulation than normal. These pains mean nothing more than poor physiological adjustment to extra demands made upon the neurons. These pains appear if the patient becomes tired, worried or unhappy. They come with changes in weather and in women at the time of menstruation.

Hemoptysis, pleurisy and sputum of tuberculous origin, if present, nearly always indicate some degree of active inflammation in the pulmonary parenchyma. While this active process may not cause sufficient toxemia to produce symptoms of the toxic or constitutional group, yet it nearly always is sufficient to produce stimulation of the pulmonary nerve-endings sufficiently to discharge reflex action and produce the motor spasm which is responsible for diminishing the motion on the affected side, and which may be detected on palpating the muscles of the shoulder girdle. Any one of these symptoms, with limited motion

of one side plus tension of the apical muscles, particularly the sternocleidomastoideus and trapezius, makes about the strongest evidence, outside of finding bacilli in the sputum, that we have for a diagnosis of active pulmonary tuberculosis.

The need of definite diagnostic criteria for determining the presence or absence of early tuberculosis caused Brown and Heise (2) to suggest what has become known as the *Trudeau Sanatorium Five Diagnostic Criteria of Pulmonary Tuberculosis* as follows: (1) the occurrence of a hemoptysis of a teaspoonful or more; (2) the occurrence of pleurisy with effusion; (3) the presence of persistent moderately coarse râles in the upper half of the chest; (4) a definite parenchymatous X-ray lesion of a tuberculous character in the upper half of the chest; and (5) the presence of tubercle bacilli in the sputum.

These five diagnostic symptoms of Brown and Heise deserve a good deal of consideration, because they are based on a study of one thousand consecutive cases admitted to the Trudeau Sanatorium. It is interesting to note that three of these five criteria on which they lay so much stress belong in group 3 of my classification. The presence of râles is due to a local disturbance caused by the disease *per se* and the parenchymatous X-ray lesion is a visualization of a local process. So all five points on which they lay the greatest stress in diagnosis are really local expressions of tuberculosis in the lung.

In my endeavor to estimate the relative value of the various symptoms of tuberculosis I have approached the whole subject from the standpoint of disturbed physiology. We must not lose sight of the added diagnostic weight which is given to the symptoms in group 3 when a general disturbance, as shown by some of the toxic or constitutional symptoms, and a reflex effect, as shown in other organs and tissues, are present. I believe that with an understanding of this relationship most doubt in diagnosis can be ruled out. Of the five criteria mentioned by Brown and Heise I would consider râles alone to be the most difficult of interpretation and the least trustworthy. I cannot bring myself to the place where I feel sure that I can always distinguish between râles caused by active tuberculosis and râles caused by other local conditions; but if these localized râles are accompanied by cough and by muscle tension, belonging to group 2, even with or without some of the constitutional symptoms of group 1, I would feel fairly positive that there was an active inflammatory process, probably a tuberculosis, present. The same thing may be said regarding the diagnostic worth of the parenchy-

matous X-ray lesion. While one who is thoroughly coversant with taking and interpreting X-rays of the chest is able to designate small pulmonary lesions as active or quiescent with remarkable accuracy, most clinicians are not; and I believe that the addition of symptoms will make the X-ray evidence much surer.

From this discussion of the subject it is evident that it is safer to rely on a diagnosis based on symptoms from the different etiological groups here mentioned than upon one or more symptoms from a single group, and it is rarely in a suspected case of tuberculosis that we fail to find representatives of at least two of the groups if we make our search with sufficient care. A diagnosis of a probable active tuberculosis could be made on the presence or a hemorrhage, in which other common causes for the hemorrhage are ruled out, and on pleurisy in which other common causes are fairly definitely ruled out, and upon a parenchymatous X-ray lesion; at the same time I should feel surer of the diagnosis if some of the symptoms of the reflex or toxic groups were present. In suspected tuberculosis I consider the analysis of the symptoms from the standpoint of their etiology as furnishing the most helpful data on which to base an opinion.

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A SURVEY OF SOME BROAD PHASES OF TUBERCULOSIS[1]

WILLIAM H. PARK

When one looks at the death-rates from tuberculosis in the English-speaking countries, he is strongly impressed not only with the fact of the great decline that has taken place, but also that it began in England and in some States in the Eastern part of the United States at about 1860 and in other places about 1880, and that for the past fifty years, with but slight temporary irregularities, it has decreased in the States in each twenty-year period about 100 deaths per 100,000 population and in England about 70 deaths. For instance, in 1855 the State of Massachusetts had a rate of 500 per 100,000; in 1875, 400; in 1895, 280; and in 1915, 150. In England the rate was 350 in 1855 and 106 in 1923. The deaths from tuberculosis in infants have been diminishing as rapidly as in adults. Thus, the actual deaths from tuberculosis in New York City were 320 in 1904 and 95 in 1924 in infants during the first year of life, and during the second year 213 in 1904 and 116 in 1924. This decrease has been occurring throughout the civilized world wherever stable conditions have been present.

Those who have been studying these changes are somewhat divided in their opinions as to their meaning. Some consider that general causes have done much more to bring about this improvement than any voluntary efforts of man. Others, while recognizing the beneficial effects of better living conditions and the involuntary immunization of the mass of the people by slight infection, still believe that the deliberate spread of information among the masses as to the means to prevent infection or, if that is impossible, to arrest it has been of at least equal value. All agree that both factors have been influential. These two English-speaking countries through these years have shared in common such influences as a stable government, improving living and working conditions among the working classes, increasing knowledge and application

[1] The HERMANN M. BIGGS MEMORIAL TUBERCULOSIS LECTURE for 1925. Delivered under the auspices of the Medical Society of the County of New York and of the New York Tuberculosis and Health Association, at the New York City Tuberculosis and Health Conference, New York Academy of Medicine, November 19, 1925.

of the laws of health, progressive public-health administration, and increasing interest by private agencies in the succor of the unfortunate and the education of the people. The World War, however, made a temporary difference between the two countries. England, owing to the submarine blockade, actually suffered from want of food as well as from the terrific strain of the war. This is shown in the death-rate from tuberculosis. It rose in England from 134 in 1914 to 192 in 1918, but in 1923, under normal conditions, it dropped to 106. In the United States, where there was no deprivation of food or general distress, there was no appreciable rise in the death-rate. In the countries on the Continent of Europe, in which the suffering and deprivation due to the war were even greater than in England, the falling death-rate from tuberculosis was more markedly reversed; for instance, in Germany, from 142 in 1914 to 229 in 1918, but back to 154 in 1922. Such facts as these prove conclusively that we are right in our conviction that there is a very direct relation between the general well-being of a people and the amount of severe and fatal tuberculosis.

It is a striking fact that the improvement in tuberculosis began soon after Pasteur published his researches proving that spontaneous generation, as ordinarily conceived, does not exist, and the fact that each fermentation in nature was due to a special microörganism, and that this was undoubtedly true of the diseases of man and animals. The influence of his teaching profoundly influenced the attitude of mankind toward the treatment of tuberculosis as well as all other communicable diseases.

Let us now look a little more closely at some of the important factors that have had a direct effect on tuberculosis itself. It was some ten years after the publication of Pasteur's work on fermentation, and after the beginning decline in the deaths from tuberculosis in some localities, that the first definite blow was struck. In 1865, Villemin demonstrated that tuberculosis was a definite and specific disease and that it is due to an inoculable virus.

In 1873, Trudeau, a victim of tuberculosis, went to Paul Smith's in the Adirondacks, in order to live out-of-doors and thus treat his disease. Instead of dying, he improved, and devoted his life to teaching his countrymen the value of fresh air, rest and the education in health which goes with a course of treatment in a sanatorium. The test which he carried out on rabbits, showing that with the same amount of infection those that were given good food and were well-housed recovered while those that were undernourished and badly housed died, was most illuminating.

The teaching of his life and work and of that of his associates, who, having gained partial or complete health under his care at the Adirondack sanatorium became devoted to spreading his gospel, have had a profound influence in giving hope to the incipient consumptive, in spreading accurate knowledge and in combatting wrong ideas as to the care and treatment of tuberculous patients.

In 1882 Koch discovered the bacillus that the research of Villemin had suggested the existence of. His brilliant and conclusive work made it possible to identify cases of tuberculosis, to use animals in experimental tests, to try out methods of treatment and prevention, and to attack with definiteness problems in the cure and prevention of tuberculosis in a way which could not have been attempted without his discoveries. The identification of the tubercle bacillus, and later of the tuberculin reaction, made it possible to establish in man and animals the presence of infection and note the response to treatment. It enabled us to try the effects of treatment on the specific germ in the test-tube and in the living body.

The fundamental information necessary to attack tuberculosis was now at hand, and in the possession of the leaders of the medical profession and of a few others. What was needed was to arouse the community to the necessity of themselves acquiring this knowledge and of profiting by it. This meant, in the first place, the education of the medical profession to their duty to acquaint the public-health authorities with information as to any cases they were treating, so that the Health Department could estimate the gravity of the problem in the area under its control, and take suitable measures to meet the danger. It meant giving to the people knowledge of the necessity of seeking advice and treatment at the time of the development of the first symptoms, of the providing by public authorities for the suitable care of the impoverished sick and of suitable preventive measures for the poor and destitute, and finally the bringing in of private agencies with their great powers for usefulness in spreading information and of supplementing the work of the public authorities.

In this vital work of enlisting the official health authorities in the antituberculosis crusade and utilizing their enormous powers for gaining accurate information as to the extent of the disease, for preventing infection, for promoting education, and for providing sanatoria for the recovery of the incipient and hospitals for the care and isolation of the seriously sick, we must give the chief honor to Hermann Biggs.

Let us stop a moment more in this first memorial lecture to summarize the work of the Health Department of New York City, inaugurated

wholly or in part by Dr. Biggs during his more than twenty years of service in it as pathologist, director of the laboratories, and as medical officer. The most important of these are the attempted registration of all cases of tuberculosis, begun in 1893 and completed in 1897, the free examinations of sputum undertaken in 1893, the educational methods, the visitation and supervision of the tuberculous poor by trained public-health nurses, the referring of needy cases to proper charitable organizations, the building of free clinics for ambulant cases, of a sanatorium for incipient cases and hospitals for advanced cases, the promulgation of regulations against spitting in public places, and finally laboratory and clinical research work on preventive measures. These measures inaugurated by him still remain those upon which we mainly depend to reduce tuberculosis. If specific cures or preventives are discovered they will be added to but not replace them. Let us now proceed to the consideration of several problems in connection with tuberculosis in which the laboratory has played an important part.

THE EXTENT TO WHICH HUMAN TUBERCULOSIS IS DUE TO THE BOVINE TYPE OF BACILLUS IN THOSE USING RAW MILK AND IN THOSE USING PASTEURIZED MILK

It was demonstrated by the work of Theobald Smith that there are two types of tubercle bacilli that infect human beings, the human type and the bovine type. We now know that cattle tuberculosis is practically always due to the bovine type, while pigs have tuberculosis set up by bovine, avian and human types. The amount of bovine infection in man depends on the amount of tuberculosis in the cattle from which the milk is obtained and the amount of raw cow's milk consumed by our children. There is no evidence that the bovine type changes to the human type while in a single human body. In countries such as Japan, where in many localities cow's milk is practically unknown, human tuberculosis exists to about the same extent that it does in other countries.

Since the work of the English Royal Commission, the German Commission, and that of the workers in the laboratories of our Department of Health, it has been generally accepted that localized pulmonary tuberculosis is practically always due to the human type. On the other hand, the glandular and the disseminated tuberculosis of infants, in places where ordinary raw cow's milk is used, is frequently due to the bovine type, and the proportion due to it is dependent upon the amount of tubercle bacilli in the raw cow's milk.

Thus Krumwiede and Park in 1911 found in the children of New York City that the bovine type of tubercle bacillus causes a marked percentage of the cases of cervical adenitis leading to operation, temporary disablement, discomfort, and disfigurement; that it also causes a large percentage of the rarer types of alimentary tuberculosis requiring operative interference or causing the death of the child directly or as a contributing cause in other diseases; and that it is not infrequently the cause of tuberculous meningitis.

They proved that in New York City in young children it becomes a menace to life, and that before the pasteurization of our milk supply it caused from 6 to 10 per cent of all fatalities from tuberculosis in children.

An interesting comparison is the proportion of bovine tuberculosis in the lymph nodes examined in 1910, before the general adoption of pasteurization, and the amount in a series tested after pasteruization had become compulsory except for certified milk. The degree of bovine infection in the lymph nodes has been found to be an index of the amount of bovine infection in the children.

BOVINE AND HUMAN TYPES OF TUBERCLE BACILLI IN TUBERCULOUS LYMPH NODES AND IN MENINGITIS IN NEW YORK CITY

Before the General Pasteurization of Milk

	Human	*Bovine*
Tuberculous meningitis	54	3
Tuberculous adenitis (cervical)	34	21

After General Pasteurization

	Human	*Bovine*
Tuberculous meningitis	48	3*
Tuberculous adenitis (cervical)	30	6**

* One a child of two years gave a history of having been fed on Grade B pasteurized milk. One 3 years old and one 8 years gave a doubtful account of milk. The 8-year old was from the country. Raw milk and butter were suspected.

** In one case the onset of the disease was in prepasteurization days and in another case, 25 years old, the infection might have been.

** One case, 2 years old, had been fed on several supplies of raw milk.

** One case, 7 years, gave a history of never being given cow's milk. Butter might have been the source.

** One case, 6 years, had Grade A raw milk and certified raw milk.

** One case, 7 months, had Grade A raw milk.

The difference between 21 out of 55 due to the bovine type before pasteurization and 6 out of 36 after pasteurization is striking enough, but it is more convincing from the further fact that one of the 6 cases certainly developed the infection in prepasteurization days, and that

another likewise probably did so and that 3 of the 4 remaining cases were fed on raw Grade A milk. Therefore, only one of the 36 children having tuberculous lymph nodes was possibly fed on pasteurized milk, and in this case the mother denies that the child drank any milk.

In 1917, Barnet reported that, in Paris, of 19 infected lymph nodes typed, none was due to the bovine bacillus. The striking difference between these figures from New York City and Paris, where the children's milk is pasteurized or boiled, and in Edinburgh, where most children consume raw cow's milk, is seen in the following figures from Mitchell, in the *British Medical Journal* in 1914:

Cervical lymph nodes, 1 to 3 years, 25, bovine type 23
Cervical lymph nodes, 3 to 5 years, 17, bovine type 16
Cervical lymph nodes, 5 to 10 years, 25, bovine type 23
Cervical lymph nodes, 10 to 12 years, 10, bovine type 3

From these findings there can be no question that at the present time pasteurization or boiling is an essential safeguard against bovine tuberculosis. A temperature of 142°F. for 30 minutes is ample to destroy all tubercle bacilli. It is still necessary for health authorities to have control over the pasteurizing plants. There is not time to go into the question of the details to be carried out for making a raw milk safe from bovine infection. Our reliance is on honest physical examination and the tuberculin test. It requires a combination of the intracutaneous and subcutaneous tuberculin tests and a determination on the part of the farmer and the veterinarian to carry out these tests in the most approved way. At the present time certified milk produced for New York City is practically safe from tuberculosis, but it is not absolutely so. At most tests of herds one or two per cent of the cows give a tuberculin reaction and, when killed, usually show slight lesions of tuberculosis.

We are trying now to use either repeated intracutaneous and ophthalmic tests, or these together with annual subcutaneous tests, and perhaps we may succeed better with these modifications and make the milk of certified herds absolutely safe. One great difficulty is to find new uninfected cattle to replace those that have passed their period of usefulness. Butter made from infected milk is dangerous for young children. Fortunately, it is becoming the custom to pasteurize all cream before using it to make butter. Fully 90 per cent of the butter in large cities is now made from pasteurized cream. Pasteurization should be made compulsory. It not only destroys infection but it improves the average flavor and keeping qualities of the butter.

THE PREVALENCE OF INFECTION WITH TUBERCULOSIS IN MAN AND ITS BEARING ON PREVENTIVE MEASURES

The discovery of the tuberculin reaction by Koch opened up a method of determining when the first infection occurs. Within a few weeks of the beginning of disease a state of hypersensitiveness develops, which can readily be detected without risk or annoyance to the patient by the Pirquet skin test or its more reliable modification, the intracutaneous test.

By means of this test we know that in most cities during the first year of life about 5 to 10 per cent of all infants become infected, and during the second year an additional 10 to 15 per cent. At the end of five years some 50 per cent have become infected, and at 15 years 75 per cent. These children not only have been infected, but they remain infected or otherwise the tuberculin reaction would not have persisted. The persistence of infection has also been shown by inoculation of autopsy material obtained from those dying of other infections or diseases. In the great majority of infants and young children the infection localizes in the nearest lymph nodes. These tubercles as a rule caseate, sclerose and then remain quiescent. If, as Krause has shown, resistance is lacking or the quantity of infection is too great, the bacilli pass beyond the lymph nodes to the smaller intravisceral collections of lymphatic tissue, where the bacilli are apt to arouse a more progressive inflammation. The tubercle bacilli, when arrested, generally remain quiescent in the lymph nodes until something causes an inflammation. This may be a tonsillitis, an attack of measles or scarlet fever, an ulcerated tooth or a cold. The absorbed poisons from these areas of inflammation flow to the lymph nodes and cause an irritation of their tissue. This causes a change in conditions in the node, which may allow the bacilli to increase in numbers, and produce and liberate toxins with the development of symptoms of intoxication. The bacilli may also disseminate to other portions of the body. Especially later in life, besides the various infections anything which produces overstrain, such as intemperance, exposure to cold, starvation, confined work under unhygienic conditions, may disturb the equilibrium between resistance and infection and an increase in the tuberculous lesion may occur.

An important element which is often decisive as to whether the added sickness or strain will cause an increase and dissemination of the tubercle bacilli is the duration of the primary infection. For the first days after

infection with the tubercle bacilli, the average body, except perhaps in early infancy, because of passive immunity has no or but little resistance to the spread of infection beyond the anatomical structure of the tissues, but within a few weeks a very considerable specific immunity develops.

Does the fact, that practically every grown-up person in a civilized well-populated country develops at some time a primary infection, make our attempts to lessen infection hopeless? I do not believe there is any reason to think so. In the first place, it is important to protect infants in their early years, for their general resistance is less than that of older children, and again the quantity of the first infection an infant receives is of the greatest importance. We know that in small animals the injection of a few bacilli will usually lead to a slight infection, which will run a subacute or chronic course and frequently result in cure, while a larger dose will usually cause a rapidly progressive tuberculosis. These different results of different degrees of infection undoubtedly occur in children. We, therefore, have the strongest reasons for continuing all the measures which have been advocated to reduce, even if we cannot prevent, the spread of tubercle bacilli from human and animal sources to other individuals. The statistics published by Drolet, as well as the small death-rate from tuberculosis under six months, indicate that the passive immunity transmitted by the tuberculous mother is a safeguard to her offspring and partly compensates for the added danger of infection. Toward the end of the first year this passive immunity probably disappears. It would be interesting to note the comparative danger of infants born of apparently healthy reacting and nonreacting mothers. It must not be lost sight of that proof is given by the tuberculin test that a considerable percentage of older children, and even a small percentage of adults, have never been infected, or at least have no present infection. Whatever may be our personal opinion as to whether or not a case with a slight infection is liable to a fresh infection from outside, we all must agree that those who have no infection are liable to it. Opie has shown that autopsies prove that a small percentage of adults die of general miliary tuberculosis without any lesions indicating a previous infection. There is nothing, therefore, in the recent additions to our knowledge which should prevent us from reducing in every way possible the quantity of tubercle bacilli spread from tuberculous people. The only difference is the fact that we now know we have less to fear from the results of infection, if those who have been so unfortunate as to develop it can early put themselves under favorable conditions.

The following observations on the danger of an infant born of tuberculous parents contracting clinical tuberculosis in infancy were made at my request by Dr. Harris, Director of the Bureau of Preventable Diseases. He was so kind as to have his nurses make a survey of the condition of 53 babies that had been born within the past 20 months in 52 families in which either the mother or father was tuberculous.

Fifty of the 53 are still living, their ages being between 3 and 20 months. Twelve per cent of these 53 babies have developed lesions, suspected or known to be tuberculous, or, to put it the other way, 88 per cent show at the present time no evidence of tuberculosis.

The mothers of 13 of the infants who had lived between 6 and 20 months are believed to be tuberculous, but in some a positive sputum was not obtained.

Ten of these babies are well, one died from unknown causes, one suffers from malnutrition, and one was suffering from acute bronchopneumonia at the time of the visit. Seventeen babies have or had tuberculous fathers, 12 are well, 2 are undernourished, 2 have tuberculosis, and one is dead of an acute illness at the age of 20 months.

Sampson (*Bull. Univ. Minnesota, 1913*) found that 67 per cent of children born of parents with open lesions became infected at an early age. Those born into families in which members showed only latent lesions showed infection in only 22 per cent, while in tuberculosis-free families it was only 2.5 per cent.

The question of the comparative immediate and later danger of infants born in families, in which a member has clinical tuberculosis and comes in contact with the baby, and infants born in families, in which no clinical tuberculosis exists, is worthy of further study. The difference is probably less than is generally believed. It is most opportune that investigators like Asserson and Drolet are attacking the problem.

SPECIFIC IMMUNITY AND THE POSSIBILITY OF PRODUCING IT ARTIFICIALLY

Our first information on this subject came from Koch. In 1891 he noted that guinea pigs, which received a sufficiently large first injection of virulent tubercle bacilli, reacted with the development of an ulcer and a progressive tuberculosis leading to death. Guinea pigs which had received a moderate injection, four to six weeks previously, when reinoculated just beneath the skin, developed very rapidly induration and ulceration. The ulcer, however, instead of progressing, soon ceased to extend, and then rapidly healed. Thus the inoculated tubercle bacilli

act quite differently when under the skin of a guinea pig already tuberculous than when under the skin of a normal animal. Koch found that injections of tuberculin and of dead bacilli would also render animals more resistant. This led him to hope that in tuberculin he had a cure for tuberculosis, not realizing that cases of tuberculosis had acquired from their disease practically all that he could give them by the injections except a tolerance to the tuberculin. It was until recently believed that immunity, with its accompanying reaction to tuberculin, could not be produced except by living bacilli; but Petroff and others have shown that injections of considerable quantities of tubercle bacilli killed by an exposure for one hour at 100°C. were able to produce true skin hypersensitiveness. Petroff noted that the bacilli must be well titrated, made up in a good suspension, and adjusted to pH 6.9 or 7. The guinea pigs must be mature. The injections are given every three or four days for several doses. Even an injection of as small an amount as 3.75 mgm. in a guinea pig can set up a skin hypersensitiveness which persists for a year. The attempts to use some kind of a preparation of dead tubercle bacilli or their toxins to increase antibodies in cases of tuberculosis have been countless. The first was that of Koch, the last important one was that of Dreyer.

In 1923 Dreyer (*Brit. Jour. Exp. Path., iv, 146*) published a new method of preparing a vaccine from acid-fast and gram-positive bacteria.

It is based upon the principle that acid-fastness and gram-positiveness are associated with the presence in the bacterium of certain lipoidal substances, which are probably the cause of failure in immunization because of their power to protect the specific bacterial proteins and to prevent their liberation from the body of the bacterium.

The method, broadly, consists in the successive applications of formalin and acetone to the bacilli.

His first published results were encouraging, but he used too few animals as controls to draw reliable conclusions. Additional support to his expectation was given by the fact that the "defatted" antigens caused no local reaction when injected into normal animals.

It seemed to him, therefore, legitimate to hope that they would prove of value. The first results in the treatment of human cases seemed encouraging. Fildes and Western were given facilities for testing these antigens at the London Hospital. They reported:

We have under treatment with Dreyer's antigen 60 cases of tuberculosis. Among these are 36 cases of tuberculous adenitis, 11 cases of cutaneous tuber-

culosis, 4 cases of pulmonary tuberculosis, both active pyrexial and apyrexial, 3 cases of joint and bone tuberculosis, 1 case of peritonitis, 1 case of tuberculosis of the urinary tract, 1 case of iridocyclitis and 3 cases of epididymitis. Most of these cases have been under our personal observation for considerable periods, up to 5 years, and have been selected for the new treatment as having shown little improvement under treatment with tuberculin B. E. (Koch).
Improvement has taken place in nearly all cases, and is, in our opinion, of an order which exceeds obviously that obtainable by any other form of treatment which is applicable to these conditions.

However, further observations did not yield favorable results, and Dreyer's vaccine has been abandoned.

IMMUNIZATION BY VACCINATION BY ATTENUATED LIVING CULTURES

A few attempts have been made to immunize animals by giving them at first an injection of a very few virulent bacilli, and then repeating the injections with gradually increasing amounts. Some fairly successful results were obtained, but the method is not a practical one.

The first attempt to immunize animals with attenuated cultures was made as long ago as 1886. In 1902 Behring developed a method of vaccinating cattle which gave quite promising results. He used a slightly attenuated human culture which possessed practically no virulence for cattle. The first injection in the treatment was of 4 mgm., and after three months a second of 20 mgm. Many practical tests were made as to the immunizing value of the vaccine.

The following is an example: A test on 20 calves was carried out in France. Two months and nine months after the completion of the treatment a vaccinated calf was killed and examined. No tuberculous infection was found. Six of the vaccinated animals and 6 controls were given large injections (4.5 mgm.) of virulent tubercle bacilli of the bovine type. All the controls developed fatal tuberculosis. Four of the vaccinated animals showed no lesions and 2 slight lesions only. The lymph nodes of all the vaccinated animals contained living bacilli of the human type. Two of the vaccinated and 2 of the unvaccinated animals were stabled for a year with tuberculous cattle. The two controls developed advanced tuberculosis. One of the vaccinated showed extensive lesions, the other but a tiny tonsillar focus. Four animals were used to test the duration of the immunity. Two were given an intravenous injection of bovine bacilli, one year after receiving the vaccine. One died of acute tuberculosis, and one developed chronic tuberculosis. Two were stabled

two years after vaccination with a tuberculous cow for thirty days. One developed tuberculosis.

The authors' conclusions were that the definite resistance developed because of vaccination exhausts itself withing the year. The animals remain very susceptible to tuberculin for 8 to 12 months. A practical difficulty is that the animals may pass the human bacilli for months by their milk and dejecta. This was considered a very real danger, and caused doubts as to the wisdom of permitting the use of the vaccine. This led a number of workers to try and get attenuated tubercle bacilli absolutely harmless to man. Calmette and Guérin discovered that, upon media made of potato, bile and 5 per cent of glycerin, a culture of bovine bacilli gradually became attenuated, so that it would not produce tubercles. After 70 transplants a calf will withstand 100 mgm. This will cause a fever for 15 or 20 days, and then a perfect recovery takes place. If autopsied, no tubercles are found. Calves which receive two inoculations one month apart will, after another month, withstand an intravenous inoculation of 3 mgm. of virulent bovine bacilli. A part of the virulent bacilli, while they produce no lesions, remain alive in the lymph nodes. This vaccine bacillus, while not virulent, has retained the property to live in the lymphatic cells. It can be obtained after months in cultures. Calves even a year after inoculation could be stabled with tuberculous cattle without developing clinical tuberculosis. A recent report by Wilbut on protecting monkeys is so interesting that I will give the results in some detail (J. Wilbut, *Annales de l'Institut Pasteur, 1925, xxxix, no. 8*).

Observations were first made by observing the effects of subcutaneous injections and absorption through the buccal tract of large doses of Calmette's attenuated bacillus in monkeys.

All stood very easily the 100 mgm. of vaccine introduced by subcutaneous means. The enormous dose produced only a slight edema at the point of inoculation. A dose of 50 mgm. or less gave no appreciable reaction, and the monkeys which succumbed to other ailments showed at autopsy no tuberculous lesions.

For the vaccination experiment a single dose of 50 mgm., subcutaneously, or by mouth in 5 doses of 50 mgm. each every two days, were given.

The vaccine was prepared as homogeneously as possible. For ingestion the vaccine was incorporated in the pulp of bananas or other fruits.

The control viruses were made from the human culture called *HR* and the bovine culture called *BV*.

In a series of preliminary experiments it was determined that the animals of all weights and all ages were infected regularly with a dose of 0.000,01 mgm. subcutaneously of *HR* or *BV* (containing about 400 bacilli); or by the ingestion of 2 doses of 0.001 mgm. each (40,000 bacilli) absorbed at 48-hour intervals. In the monkeys thus infected death occurred generally in from three to six months. With stronger doses, 0.1 mgm. of *BV*, subcutaneously, caused lesions resulting fatally in four to six weeks.

The main object of the final experiment was to protect vaccinated monkeys against infection when in close and continual contact with infected monkeys.

The experiment was begun February, 1924. In all, 15 chimpanzees and 59 petheciens were used.

The conclusions were

1: The inoculation and ingestion of Calmette's culture up to 100 mgm. show no harmful effects.

2: The chimpanzees and petheciens of all ages can be easily immunized by single subcutaneous inoculations of 50 mgm. of *BCG*, or by 5 ingestions (each of 50 mgm. in 8 to 10 days), against tuberculous infection by exposure to a continuous and close contact with artificially infected monkeys.

3: The first immunization, thus conferred, has lasted over one year.

4: It can be maintained by a second inoculation or by new ingestions via the buccal tract repeated each year.

Calmette came to the conclusion that the work done on cattle and monkeys indicated that he had in his attenuated bovine culture a virus that would be absolutely without danger in human beings of all ages, and that it held out great hopes that it would immunize infants. In the first six months of 1922 he injected 178 infants born of tuberculous parents. During the past three years none of these has developed tuberculosis. Fifteen have died from other diseases. A considerable number of these children have remained in the same homes as their tuberculous parents, but none of these show any evidence of tuberculosis. The vaccine has been given to the infants in a teaspoonful of milk half an hour before giving them food. The feedings have been on the fourth or fifth, the sixth or seventh, and the eighth or ninth days after birth. During the last twelve months, 2,070 infants born of tuberculous parents have been given the vaccine treatment in Paris or in other parts of France and Belgium. Up to June 1, 1925, Calmette had traced 423 of these infants for a period of six months or longer, and none of them had died with any evidence of tuberculosis. Two cases had died of meningitis, but the

histories did not suggest a tuberculous origin. Calmette and his associates are now making a careful study of the percentage of infants born of tuberculous mothers who develop tuberculosis and die from tuberculosis, to compare the morbidity and mortality of these cases with those born and reared under similar conditions who have received the vaccine treatment.

He estimates that 25 per cent of infants born of tuberculous mothers and reared by them at home die of tuberculosis during the first year of life. This estimate is higher than our records show, but there can be no doubt of the high mortality from tuberculosis during the first year.

Calmette draws the conclusion from his work that the treatment is certainly safe, that it has given evidence in animals of producing immunity for at least a year, and that this can be lengthened by annual treatments.

The vaccine in infants has certainly proved to be harmless, and the results seem most promising in that none of the 400 infants of tuberculous mothers, or at least in tuberculous families, that have been followed up for a period of six months or more, have shown symptoms of infection or have died from tuberculosis. I believe that the evidence is sufficient to make it our duty to test out his vaccine first in calves and later in infants, so as to make a careful trial of the vaccine as an immunizing agent against tuberculosis in infants. If successful, the vaccine should also be tried in older children who show no tuberculin reaction. We have started experiments to test his claims on calves, monkeys and small laboratory animals.

CHEMOTHERAPY

Chemotherapy is well defined by Moellgaard as the introduction into an infected organism of a substance having a directly injurious influence on the parasite, and forcing this influence upon the parasite at long distances from the place of introduction. The possibility of such effect is intimately connected with a specific affinity of the substance for the parasite. Without such affinity it is hopeless to attempt to influence the parasites in any generally infected organism by means of chemical agents.

A substance which is poisonous to a parasite will also exercise some toxic effect upon the infected organism.

Every injection of a chemical substance into the blood of any human being, therefore, always implies some risk, which must be balanced against the risk of giving no chemotherapeutic treatment.

The peculiarity of the tuberculous tissue, which is of importance in chemotherapy, is its poverty in blood-vessels. This means that a chemical compound must diffuse from the blood through the tissue to reach the tubercle bacilli, and the distance through which diffusion must take place grows longer as the tubercle increases in size and develops in caseification. Whether a chemical compound under these conditions reaches the bacilli or not is a question, not only of its more or less pronounced specific affinity, but also of the ratio of its diffusion velocity to the velocity with which it is decomposed in or excreted from the organism. The hope for chemotherapy in tuberculosis is therefore probably intimately connected with the possibility of finding a substance which diffuses very quickly through animal membranes, and which is sufficiently stable in the organism to be kept unaltered in the blood and the lymph for a relatively long time. For many years efforts have been made to find some chemical which would destroy the tubercle bacillus without destroying the cells of the body. The latest of these is Sanocrysin. The heavy metal carried by the Sanocrysin ion is gold. Previous investigations showed that it exercises a great influence on tubercle bacilli in culture. To act as a chemotherapeutic agent the complex ion must be able to carry the gold through the lipoid matter into the bodies of the bacilli.

So far Moellgaard has found the Sanocrysin ion to be the body which best fulfils this condition. The chemical constitution of Sanocrysin is believed by Moellgaard to be written very probably as follows: $(AuS_2O_3)^{Na}_{Na_2}S_2O_3$. In watery solution it dissociates according to the equation: $AU(S_2O_3)_2Na_3 = 2Na_3 = AuS_2O_3 + S_2O_3 + 3Na$. Its therapeutic agent is then the complex negatively charged ion AuS_2O_3.

Shock Produced by Sanocrysin: Very early in his experiments Moellgaard found that one-third of the Sanocrysin dose, which is tolerated by the healthy guinea pig, always produces very severe intoxication in the highly tuberculous guinea pig, and usually kills the animal in sixteen to forty-eight hours. In calves, which ordinarily do not die until forty-eight hours after the injection of Sanocrysin, the development of the shock was investigated in detail. Ordinarily it begins with albuminuria, which develops into a grave parenchymatous nephritis.

The third and last stage in the intoxication in animals affected with pulmonary tuberculosis is an extensive oedema of the lungs.

Curative Results Claimed by Moellgaard: The general results of the animal experiments hitherto made may be summarized as follows: The combined Sanocrysin and immune-serum treatment has saved the life

of even very gravely infected goats, calves and monkeys, and brought them into a condition of clinical healing.

The reports of the use of Sanocrysin in the treatment of human pulmonary tuberculosis emanating from Denmark were, on the whole, quite favorable. There were indeed fatal results in some and no improvement in some. Others were believed to have improved far more than they could have improved without having been helped by the Sanocrysin. Under these impressions of a successful result Moellgaard decided to make it available to all who wished to use it.

The optimistic reports of the use of Moellgaard's Sanocrysin coming from Denmark and from England stirred up a great deal of interest in the United States. Members of the Medical Research Committee of the National Tuberculosis Association and of the Public Health Service believed that some experimental work should be done before allowing it to be used in the treatment of human cases. At a conference Dr. Schroeder, representing the Department of Agriculture, Dr. Theobald Smith, representing the Rockefeller Institute, and myself, representing the New York City Health Department, were asked to conduct a series of experiments. All the results were similar. I give only a brief outline of the work done under me at Otisville.

Twelve calves were selected, and were paired so that each 2 would represent the same age and weight. All 12 of the calves were inoculated with a dose recommended by the authorities in Denmark; 6 of the calves were left as controls. The other 6, when they developed signs of beginning infection, were started with the treatment of Moellgaard's Sanocrysin and, when necessary, injections of the antitoxic serum. The treatment followed the directions sent to us. So far as the clinical results were observed, the calves on the Sanocrysin did worse than those that received no treatment. In every case but one the treated calves died earlier than those untreated. In order that observations might be made on the pathological lesions of the treated and untreated calves, Dr. Pappenheimer undertook the examination of portions of tissues from several of the treated and untreated calves. He makes the following conclusions at the end of the detailed autopsies and histological examinations:

With the exception of calf no. 3, in which the tuberculous lesions in the lungs were slight, and complicated by some other respiratory infection, all the calves, both treated and untreated, showed very extensive pulmonary lesions. There was, however, a rather definite difference in the histological type of lesions in the two groups. Whereas, in the untreated controls there was dis-

tinct tubercle-formation, with a reacting tissue of epithelioid and lymphoid cells, in the treated animals the tuberculous lesions were of the exudative or pneumonic type, progressive, and with no limiting zone of reaction. The same distinction was observed, though less strikingly, in the lymphatic lesions. This contrast in the type of lesions was very evident also in the gross, in the case of calves nos. 6 and 7, which I had the opportunity to observe at autopsy. The tubercles in the control animal were shotty, sharply localized, translucent and elevated; in the treated animal, more opaque, caseous and flat.

Tubercle bacilli were found in all cases, both control and treated. They were, however, on the whole more numerous in the treated animals. Thus in calf no. 6 (treated), they were present in enormous numbers, whereas in the control calf, no. 7, they were found with difficulty.

In 2 of the treated animals, there were indications of injury to the kidney. In one there was actual necrosis of some of the tubules; in another, less intense degeneration; in both, an albuminous precipitate distending the capsular spaces and tubules. Whether this is to be attributed to the toxic action of the gold salt cannot be stated without further experiment.

So far as the histological examination of the material from this experiment goes, there is no evidence that the treatment destroyed the tubercle bacilli in the tissues, or restrained the development of the tuberculous lesions. These results indicate that great caution should be employed in using Sanocrysin.

ARE TUBERCLE BACILLI BECOMING ON THE AVERAGE LESS VIRULENT IN PEOPLE LIVING UNDER GOOD CONDITIONS?

There are few definite proofs of this, but I believe it to be so. It is a known fact that many forms of bacteria increase or decrease in virulence, according as to whether they have or do not have the opportinity to continuously grow in the sick and produce acute and serious disease. For instance, before we acquired our present knowledge concerning the spread of infection, certain persons were known to leave a trail of sepsis as they passed from one maternity case to another. This is now known to have been due, not so much to their exceptionally bad technique, but because they were the carriers of streptococci so virulent that a single pair of germs might infect. It is possible in rabbits to raise the virulence of a human type of streptococcus by giving the first animal so large a dose that, although they are only slightly virulent for the rabbit, still they produce septicemia. A culture made from its blood will infect the next animal with a somewhat smaller dose. After a number of such transfers the streptococcus is found to have increased enormously in virulence, so that a one hundred-millionth of a cubic centimetre of the

broth-culture will kill rabbits, while formerly 0.1 cc. was required. This culture, when allowed to grow uninterruptedly on culture media, will gradually lose its virulence.

One English investigator, Tulloch, has shown that, if mice suffering from what will prove to be a fatal paratyphoid infection, but not yet sick from it, are brought in contact with and removed from contact with fresh mice before they themselves have developed symptoms, that is, while the infection is incubating and they are merely carriers, and the second batch of infected mice are brought in contact in the same way with another lot of fresh mice, while they are carriers but before they have developed symptoms, and this experiment is repeated several times, soon the fresh batches of mice will not sicken, so long as they are kept under wholesome conditions. They simply become carriers, and continue by contact to make other mice carriers. The bacilli have become attenuated by being transferred from mouse to mouse before they had had a chance to grow in the tissues of the mouse.

We have recently discovered that diphtheria bacilli in the healthy throats of carriers, who obtained the germs not from cases but from other carriers, are of little danger to those carrying them or to others in spite of the fact that they are toxic for guinea pigs. They still make toxin, but they have largely lost their power to invade and attack normal mucous membranes. The same is true for the hemolytic streptococci of sore throats and of scarlet fever. When they grow on the healthy mucous membranes of immune persons they gradually lessen their power to produce infection when in contact with the normal mucous membranes of nonimmunes.

It is true that there is less evidence that this loss of virulence occurs in this way in certain germs such as typhoid bacilli. Yet, even here in carriers of long standing, we have noted changes in the cultures, and the cases of disease that develop from carriers are usually milder than when caused by infection from cases of typhoid fever.

In tuberculosis we have some definite evidence that the tubercle bacilli in mild quiescent cases are less virulent than in severe progressive ones. Cultures from chronic skin infections have occasionally been found to be decidedly less virulent in animals than the ordinary cultures. We are handicapped by the necessity of estimating human virulence by tests in animals. Just as a diphtheria bacillus from a carrier case is fully virulent for a guinea pig and yet is not virulent for man, and a scarlet-fever streptococcus from a carrier makes potent scarlet-fever toxin and

yet is hardly able to produce scarlet fever in man, so the fact that only a small percentage of tubercle bacilli from chronic mild cases are shown by animal tests to be of less than average virulence does not prove that there is no real average difference in infectiousness and virulence in man between the bacilli of cases of quiescent tuberculosis and of rapidly fatal cases. I expect to start an experiment which I hope may prove or disprove the truth or falsity of this supposition. A few rabbits immunized by the Calmette strain will be infected with a small dose of moderately virulent bacilli of the bovine type. These will be autopsied after several months and the culture obtained will be reinoculated in partially immune rabbits. Other nonimmune rabbits will be inoculated with a large dose of virulent bacilli. From time to time new rabbits will be inoculated from these. In the course of years, it is hoped that the strain living in partially immune rabbits will lose somewhat in virulence, while the strain multiplying rapidly in the nonimmune rabbits will increase its virulence. This probable attenuation would seem to me to help account for the gradual decrease in the average severity of cases, especially among infants and young children in the United States.

If this decrease in virulence be true, we have one more reason for doing all in our power to build up the resistance of the people, and to remove progressing and advanced cases to hospitals. In this way infection, when it first takes place, will be as a rule from mild and inactive cases. If this reasoning be true, every gain in average health lesssens the number of serious cases and so causes a minute average loss in virulence of infecting tubercle bacilli and every loss in average health results in a slight average increase in severity of cases and virulence of the bacilli.

In this country we also have evidence that beyond any effect of racial changes we are gradually obtaining a more resistant population. While we continue to seek for elusive chemical agents, which will exert a deadly action against the tubercle bacillus but not against the body cells, or to practically use attenuated cultures or other means to specificially immunize, we have the encouragement of knowing that every means that will help to develop health of body and mind in the people will not only aid in increasing resistance to infection, and so the prevention and cure of clinical tuberculosis, but perhaps will also bring about the gradual lessening of the virulence of the tubercle bacilli themselves. It is possible, therefore, to hope that even if we are unsuccessful in obtaining specific chemical substances or serum antibodies we may still by our present measures succeed in vanquishing human tuberculosis.

TUBERCULOSIS AND HOUSING[1]

VLADIMIR ČEPULIČ[2]

Newsholme has shown that the improvement of housing conditions and decrease of overcrowding in apartments are, in most cases but not always, running parallel with the recent decline of tuberculosis; and he adds that improved housing conditions do not always prevent an increase of tuberculosis. In his monograph, *Gross-Stadt-Wohnungen und Kleinhaussiedelungen*, Flügge stated that dwellings cannot be the cause of a greater spread of tuberculosis in cities, because the mortality of young people from 15 to 25 years and of women, who are spending most of their time in houses, is much smaller than the mortality of adults, who follow their business outside of their homes. From the fact that the tuberculosis death-rate has decreased much more in cities than in rural communities during the last few decades, while housing conditions remained practically unchanged, we may conclude that one cannot attribute a great influence in the decrease of the tuberculosis mortality to housing conditions. Flügge denied also the value of different local statistical investigations concerning the influence, on the mortality from tuberculosis, of ventilation (Dara-Mair), air and light (Jouillerat) in the dwellings, because these researches do not take into consideration other circumstances which might influence mortality.

In my investigations as to the influence of housing on the development and propagation of tuberculosis I used the method of direct observation; that is, I investigated how a single home influenced the health of its inhabitants and whether the dwelling was in any way a causative factor in the development of tuberculosis.

In the tuberculosis dispensary of Zagreb (a city with a population of 130,000) I charted every death according to single houses, including all data available from the official records of the city. In this way each

[1] Presented at a session on *Home Supervision and Control of Contacts*, before the Sociological Section of the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 6, 1926.

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card showed all deaths that had occurred in the period 1900–1925 in every single house. We investigated especially the houses in which, during these 25 years, a greater number of people had died from tuberculosis, and especially those in which we found that several persons of the same family had died in the same flat. These are houses, which, at first glance, give an impression of their being infected (as it is said in the literature); that tuberculosis is endemic in them and finds new victims daily, not only among the population living in them for a longer time, but also among people who are moving into them as new inhabitants. They are the so called breeding-places of tuberculosis, and tubercle bacilli seem to flourish in them. The results of this work cannot be discussed in detail here, but they will be published later.

This investigation will answer the following two questions:

First: Do poor, wet, unclean flats without sun and light make for a high tuberculosis death-rate?

Second: May flats in which phthisical persons have lived communicate the contagion to new inhabitants even after such flats have been cleaned with soap and water?

We found that, in such poor, wet flats, deprived of light and ventilation, whole families will sometimes die of tuberculosis. Into such a flat, after it was quite simply cleaned and the floor washed with soap and water, new families were moving, and living under equal or similar circumstances. Some children were born there or had moved into them in infancy, and all the inhabitants remained healthy, and we found negative tuberculin tests among them. We often found that, in poor, unclean, dark and overcrowded flats, if there was no source of infection, no cases of tuberculosis developed; while in the same houses and with people living under similar circumstances, in a good flat but in family contact with a case of tuberculosis, we have had several cases of sickness and death from tuberculosis. It is known that among rich people in good flats there are sometimes several cases of tuberculosis, while, on the contrary, many healthy families are living in incredibly poor flats. We have very often seen houses, in which wet, dark flats without sun or light are without a single case of tuberculosis, while in the same house, in sunny, dry flats we find several cases of death from tuberculosis in one and the same family that lives in much better circumstances. We could often observe that children, who were born after a source of infection was removed from a flat, remained healthy

under the same social conditions, while heretofore all children of that family in the same poor and wet flat died from tuberculosis.

We also noticed cases of families, in which there were several cases of tuberculosis, moving several times from one flat to another. There were among them a few good flats, but they were mostly poor. Healthy families moved into flats, from which other families removed suffering from tuberculosis, after the flats were quite simply cleaned and the floors washed with soap and water; and these new families remained healthy for whole decades.

I think that such direct observations offer the best proof,—or, we can say, the best experiment,—in reply to our questions. The reply would be as follows: Poor flats, without sun or light, and humid, unclean and overcrowded, are not the cause of so many cases of tuberculosis in them; nor are they the cause that tuberculosis is so widespread in them. If in such flats, or in clean, light, sunny and dry ones, cases of tuberculosis occur, there must be, or must have been, in this flat or in its surroundings, a source of tuberculosis, a careless phthisic, who is or was exposing the inhabitants of the best as well as of the worst flat to frequent and abundant infections. If this source of infection is removed, we do not find, either in such poor or in the best flats, any new cases of tuberculosis.

To the second question Flügge has already replied. On the basis of his and his collaborators' experiences, Flügge thinks that for the disinfection of a flat, which was left by a phthisical person, a simple cleaning with soap and water is sufficient. Flügge admits that a few bacilli perhaps remain; but they do not suffice for an infection by contact, and, compared with other chances of infection, which are pretty abundant, such an infection with a minimal quantity of bacilli would be a real curiosity. Our observations, which I pointed out above, confirm Flügge's opinion. Flats without sun or light, which are wet, unclean and overcrowded, and in which one or more phthisical persons or even whole families have lived or died, do not constitute a source of new infections for families moving into these flats after the latter have been cleaned only with soap and water.

We must, once and for all, give up saying that some houses are breeding-places of tuberculosis; that tubercle bacilli are flourishing in them (Wernicke); that there are houses which are so much infected that tuberculosis is endemic in them and seeks new victims every day, among both the old inhabitants and the people who have moved into them recently

(Jouillerat and Louis Bonnier). We must give up believing that dark and unclean flats are a good ground for the existence of tubercle bacilli (Marie-Davy), and that the lack of light is more important for the development of tuberculosis than are overcrowded flats (Jouillerat).

Briefly, tuberculosis is not linked up with houses or flats; it is linked up with foci of disease.

THE TYPES OF TUBERCLE BACILLI IN HUMAN TUBERCULOSIS[1]

LYDIA RABINOWITSCH-KEMPNER[2]

First of all, I desire to express my high appreciation and sincere thanks to the Committee of the National Tuberculosis Association for their courtesy in extending to me an invitation to attend your convention and read a paper before this assembly.

The pleasure I take in following this invitation is further enhanced, inasmuch as it awakens in me memories of the time when, at the beginning of my scientific career thirty years ago, I had the privilege of addressing the Society for the Prevention of Tuberculosis at Philadelphia, where I discussed for the first time the acid-fast bacilli which I had then discovered in butter. And, in determining upon the types of tubercle bacilli found in man as the subject of this paper, I was partly guided by a desire to honor your esteemed President, Doctor Theobald Smith, who was the first to call attention to this important question in 1896, and partly by the fact that ever since 1901,—therefore for twenty-five years,—when my great teacher, Robert Koch, delivered his well-known lecture in London, I have been working on this problem without interruption.

A very extensive literature has sprung up on bovine tuberculosis in relation to man—concerning the question of types—and a particularly large part of it has been contributed by American and English authors. I do not intend here to dwell upon all of these works; rather I would ask to be permitted, after citing a very few figures, to report exclusively on the research I have been carrying on for the past six years, since it contains quite a few interesting contributions.

That human infection can be caused, not only by the *typus humanus* but by the *typus bovinus* as well, and occasionally even by the *typus avium* of the tubercle bacillus, is now an established fact. Nevertheless,

[1] Presented at a session on the *Biology of the Tubercle Bacillus* before the Pathological section of the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 7, 1926.

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it is important to go on gathering ever-increasing material bearing upon this question, so as first to ascertain the *frequency* of human infection with other types of the tubercle bacillus. Besides, the possibility of transmutation from one type into another is a question requiring ever-renewed consideration. For, as Orth puts it, if there be modifications, that is, forms of transition of this type, and if from some of these modifications typical forms can be produced artificially, then the bovine and the ordinary human bacilli cannot be classified as two different species; and, quite apart from the typical tuberculosis of man, no sharp distinction can be made between human and bovine tuberculosis, which means that the doctrine of the unity of human and bovine tuberculosis has to be restored, and we can speak no longer of two different, if related diseases, but merely of individual modifications of the same disease.

However, until this question has been definitely settled, we must be guided by observations showing the relative frequency of the various types of tubercle bacilli found in the tuberculous organs of human beings, and in this connection it is of the utmost importance to make a study of deviating nontypical cases as well.

Park and Krumwiede, in classifying 1,500 cases of tuberculosis (among them 478 examined by themselves), found that 1,363 had been caused by human and 173 by bovine bacilli. In 11 cases both types were found. Among the tuberculosis cases of human individuals bovine bacilli were determined as follows:

	per cent
Up to 5 years	26.5
From 6 to 16 years	25.0
Over 16 years	1.3

According to the data presented by Griffith in 1920, out of 1,068 cases of human tuberculosis (by 1923 their number had risen to 1,200) 803 showed the *typus humanus* and 194 the *typus bovinus*, 5 were mixed cultures of both types, and the balance was made up of atypical forms.

Among the tuberculosis cases classified by Kossel in 1920, 1,167 were caused by human, 120 by bovine and 3 by avian tubercle bacilli. In 7 cases both human and bovine types were found.

Finally, I should like to mention a classification by Möllers, comprising 1,861 cases of human tuberculosis. Among them, 1,704 were caused by human, 154 by bovine, 13 by mixed infection by both types, and 3 by avian bacilli. In his classification, however, Möllers has failed to consider the atypical bacilli, included by some authors, since they did not fit into his rigid classification.

The type of bacillus causing tuberculosis in birds has likewise been isolated in a number of cases of human tuberculosis. In this respect there were already available experiments of earlier date by Pansini, Kruse, Nocard, Löwenstein, Koch and Rabinowitsch, Fansco and Elfer, and others,—about 20 cases, all told. More recently, Löwenstein of Vienna has been particularly prominent in calling attention to the fact that avian tubercle bacilli are found in human patients, especially in renal disease, and in cases described as *typhobacillosis Landouzy*. A monograph, published this year by Plum at Copenhagen on *Avian Tuberculosis in Mammals* contains a very valuable compilation of the entire literature on this question.

Very interesting are the observations showing that the pregnant uterus of cows is a preferred spot for avian tuberculosis. Very frequently miscarriage ensues; in fact, it was in cases of such miscarriages that Plum, in his histological investigations of the placenta, ran across the tubercle bacilli. O. Bang has also furnished detailed descriptions of such tuberculous changes. According to Plum and Bang these are pure cases of ingestion tuberculosis, exactly as in swine.

Avian tuberculin produces strong reactions in this paratuberculosis of cattle as well, and it should therefore be more often applied in cattle, at any rate in cases in which the diagnosis is doubtful.

It is a well-known fact that tuberculosis has vastly increased in Germany as a result of war and postwar conditions. The decline of mortality, which was noted especially in infancy during the last decade before the world war, first came to a halt during the war, and was then followed by a renewed and thus far permanent increase. According to Umber's data, based on the experience of the hospital at Charlottenburg, infants aged from 1 to 3 months, as early as during the war, were showing positive cutaneous reactions, a circumstance which had never been observed in prewar times. Children at ages of from 3 to 6 years contributed a relatively high percentage to the cases of tuberculous infection, and 70 per cent of the infected children at ages 5 and 6 became diseased and manifestly tuberculous. Moreover, tuberculosis at ages 2 to 10 resulted far more frequently in death.

Even worse are Kessler's figures. In a small town with rural environment, after the war every second child over 6 years of age, and at the earliest ages of life every third infant, were found infected with tuberculosis. It is remarkable that in a city like Rostock the extent of tuberculous contagion after the war exceeded that of Vienna before the

war. All the other statistics tell the same story—infections begin at extraordinarily *early* ages, and babies and small children contribute the highest percentages to the *fatal* cases of tuberculosis.

In collaboration with Hart, I showed, as early as 1916, that during the war-years 1915 and 1916 the cases of primary tuberculous infection of the intestines in Berlin children had trebled. The material contributed by Hart from the hospital at Berlin-Schöneberg showed that, figured on the basis of all cases of infantile tuberculosis in 1916, 44 per cent were primary intestinal tuberculosis, while former years had only shown from 5 to 8 per cent incidence.

As to cheesy tuberculosis of the mesenteric lymph glands, induced by primary intestinal infection, and as to tuberculosis of the intestine itself, this investigation showed that in no less than 83.3 per cent of all such cases included in it the disease was caused by the *typus bovinus*.

The cases just mentioned, which were examined by Hart and myself jointly, were followed by 5 more cases of primary intestinal tuberculosis. Hart's materials,—the fully prepared mesenteric lymph nodes,—came in one case from an adult, and in the other 4 cases from children aged from 3 to 8 years. The primary tuberculosis of the adult was due to infection with a typically human strain of medium virulence; of the 4 infantile cases one was caused by a human type, and 3 by bovine types. All of the 3 bovine types showed the characteristic sparse and thin films *on* the surface of fluid cultures; they formed exclusively alkali, according to Theobald Smith's method of differentiation. The usual doses inoculated into rabbits regularly produced generalized tuberculosis.

Furthermore, I should like to report the results found in examining 20 specimens of dissected material from the Moabit Hospital, which Professor Benda suspected of infection by bovine or atypical bacilli. Most of the material received for examination,—in the majority of cases mesenteric lymph nodes besides other tuberculous organs,—was used to originate cultures of bacilli, and some of it was inoculated into guinea pigs and rabbits. The cultures thus propagated were tested for their biological properties and their virulence when inoculated into guinea pigs, rabbits, and in some cases also hens. Unfortunately, the very modest funds available to me for scientific research did not permit experimentation on large animals.

Among the 20 cases examined there were:

11 cases of primary intestinal tuberculosis, and

9 cases of other tuberculous localizations, most of them affecting the abdominal organs as well.

Among the latter there was one case of dermatomyositis, which I should like to discuss last and in detail. Of the remaining 19 cases one is eliminated, since the examination of the suspected organ, a calcified mesenteric lymph node, showed no tuberculosis either in the cultures grown from it or by animal experiment.

Brief mention may be made here of the findings in a second case referred to me by Professor Benda as suspected of tuberculosis, inasmuch as dissection showed a metapneumonic empyema. The cultures propagated in this case from the lung failed to show tuberculosis; but the acid-fast bacteria which had already been found in coverslip preparations, developed into cultures, reminding me of the culture of acid-fast rod-shaped paratubercle bacilli I had grown from gangrenous lung tissue in 1900. Guinea pigs inoculated with the original material in this case remained alive, and, when killed some months later, showed no trace of any changes. Nor did inoculations of salt-solution suspensions of pure cultures grown from it produce any changes in the experimental animals. But intraperitoneal inoculations of guinea pigs with cultures of the first generation in suspensions of sterilized butter mostly produced the changes described for paratubercle bacilli from butter. I do not propose, at the present moment, to go into further details about this type, or to decide the question whether it must merely be looked upon as an incidental finding or whether it caused the changes produced. I just want to mention it here, on the chance that it may tempt someone to make further investigations in that direction.

Of the remaining 17 cases, I was able to isolate typically human tubercle bacilli in 10, and typically bovine strains in 6 cases. In one case the culture was atypical; in the first two generations its growth was very sparse, but continued subcultures developed more abundantly later. This strain proved pathogenic for rabbits, but with attenuated virulence. Even after passing three or four times through the body of a rabbit, its virulence was not raised. This atypical culture, which may perhaps be looked upon as an attenuated bovine type, was propagated from the mesenteric lymph node of a young woman (19 years old) suffering from chronic pulmonary, intestinal, and lymph-node tuberculosis. Unfortunately, my examination in this case was confined to a mesenteric lymph node showing fresh tuberculous changes. No specimens from the lungs or intestines were examined, and there accordingly remains a possibility that these organs might have been found to contain more typical bovine types.

I shall now proceed to the last case of this series of my investigations, and I should like to discuss it somewhat more in detail, because the findings are unique in many respects. In the *Zeitschrift für klinische Medizin* (*1925, Bd. 102, H. 2/3*) Dr. Grunke, Senior Physician of our hospital, has already published a clinical report on this, a case of dermatomyositis caused by tuberculosis. In 1924 Professor Benda discussed the case from the pathological point of view at a session of the Association of Central German Pathologists at Dresden. The bacteriological examination of the case was made by me and completed only a short while ago, and I should like, therefore, to give you a new summary of it.

The patient was a miller, 55 years of age, whose family history contained nothing out of the way. Clinically the disease presented itself as a feverish exanthema and swellings of the limbs, resembling erysipelas, with solid infiltrations which could be felt underneath the skin, new spots forming as existing ones receded. No clinical evidence of pulmonary tuberculosis was detectable. The tuberculin reaction was positive. Seven months after entering the hospital the patient developed a dry pleurisy, which after another month caused death. The autopsy, performed by Professor Benda, showed a *single* focus of disease in the lung, about the size of a hen's egg, a *single* cicatrizing tuberculous ulcer of the ileocaecal valve, and calcareous foci in the hilum lymph nodes. There were, in addition, an exudative tuberculous pleurisy and the peculiar skin-muscle disease. Large stretches of the skin, especially of the upper extremities, showed reddening and brown pigmentation of the epidermis and subcutaneous edema. Microscopically, there appeared connected, largely caseated tuberculous infiltrations, grouped especially around the veins and lymphatic vessels. A test excision, 7 months before, had revealed similar findings.

The *pathologico-anatomical diagnosis* was as follows: Slight chronic tuberculosis (pulmonary and intestinal), pleurisy of both lungs, *tuberculous dermatomyositis recurrens.*

Of this case of tuberculous phlegmon of the fascia I received for bacteriological examination one piece each of the lung, the skin-muscle and the intestinal ulcer. These organs were used both for starting cultures and for direct inoculation of guinea pigs and rabbits. I was able to obtain the three cultures both directly from the respective organs and by passage through animals. For over two years I have studied these three cultures and a number of subsequent generations produced by passage through animals, and am only now able to express a definite opinion concerning my investigations.

The cultures grown from the lung and the intestine were identical; they behaved alike both as to growth and pathogenic properties. According to characteristics of growth, especially in the first generation, they are bovine tubercle bacilli. Rabbits, inoculated with the usual doses of these cultures, showed at autopsy tuberculous changes of the sites of inoculation, the lungs, kidneys, lymph nodes, and occasionally also of the spleen. Nevertheless, the rabbits remained alive for months (from 3 to 6 months) in some instances. The progress of the disease was slow and chronic. Guinea pigs inoculated with this culture also died of tuberculosis, but with them too, especially in the first generations, the disease did not progress very rapidly. These cultures were of the bovine type, but of less than typical virulence. Such cultures of the bovine tubercle bacillus have been described by various authors in connection with cases of lupus.

Now for the culture grown from the skin. In the first generation, whether isolated immediately from the skin or from organs of guinea pigs, the growth was rather slow; but even at this early stage this culture was to be distinguished from those described above by a creamy, moist layer suggesting avian tubercle bacilli. I therefore soon started tests on fowls as well. These tests proved positive. For guinea pigs this culture, by direct inoculation of the skin, was shown to be of slight virulence; and even after repeated reinoculation of the infected organs no materially increased virulence was noted. Most of the subsequent generations of this culture produced a slowly progressing tuberculosis in inoculated guinea pigs. Only after repeated passages through the bodies of fowls did the strains show almost no virulence for guinea pigs. For rabbits the culture was pathogenic. In the organs of the latter great collections of acid-fast bacteria, of the kind usually seen in avian tuberculosis, could be demonstrated in every case. But here too the progress of the disease was slow, and some of the infected rabbits survived for months.

The cultures grown from the lung and the intestine of the above case produced no changes in fowls inoculated with them.

In reviewing my own observations I come to the conclusion that the three cultures propagated from the case of dermatomyositis behaved differently. The cultures from the lungs and the intestine, respectively, behaved like attenuated bovine bacilli, while the culture from the skin showed all the characteristic marks of avian tubercle bacilli, except

for its relatively higher virulence with respect to guinea pigs. There are (*cf.* O. Bang, *et al.*) bovine cultures which are virulent for fowls, and this made me think at first that this culture from the skin might be of the bovine type; my experiments, however, showed me that such was not the case. The avian tuberculosis culture, which Löwenstein isolated from sputum in 1905, was likewise more virulent for guinea pigs than avian tubercle bacilli usually are.

In my opinion it can hardly be assumed that in this case of dermatomyositis the infection had been caused by two completely different types. Rather I believe that the original bovine bacilli, which had long been harbored in the body of the patient, were responsible for the dermatomyositis as well. Apparently the oldest tuberculous focus was located in the intestine. I assume that the weakly virulent bovine tubercle bacilli were carried *via* the blood-vessels from the tuberculous foci within the body to the skin, and there were changed in their characteristic properties under the influence of conditions unfavorable to them, thus passing through a process of transformation.

Strümpell has called attention to the significant coincidence of dermatomyositis with pulmonary tuberculosis, and the possible connection existing between these two diseases. It would be very interesting to have more cases of this kind investigated, with a view of ascertaining whether they are always due to tuberculous infection, which type of tubercle bacillus causes the infection, and whether deviations from the typical behavior can be demonstrated in every case.

It is a well-known fact that in the classification of types the avian tubercle bacilli are more nearly related to bovine than to human bacilli.

In considering my findings, I was reminded of the experiments of O. Bang, who succeeded in transmuting cattle tubercle bacilli into avian ones, not only with respect to growth but especially in regard to their pathogenic properties. Following this lead, I have tried to pass the cultures propagated from the lung and the intestine of the above case through the bodies of hens and rabbits, to see whether I could attain a transmutation of these cultures. I regret that, because of insufficient supply with animals for experimentation, my experiments could not be as comprehensive as perhaps they ought to have been; and, moreover, they did not include any experiments on larger animals. Accordingly, the cultures have not changed, under my observation, beyond growing very profusely on the culture-medium, as a result of the numerous reinoculations, so that they looked like human tubercle-cultures. That

old cultures of bovine tubercle after many reinoculations will grow like those of the human type is, of course, a well-known fact.

Now, with a view to getting nearer to the problem of the transmutation of types, I have tried to test the effect of the various rays on both the cultures generated from the above-mentioned case and on tubercle-bacillus cultures of other origin. This series of investigations, which I started in collaboration with Dr. Frick, has not yet been concluded.

The question of experimental transmutation of the various tubercle bacilli from one into another, is one that I shall not dwell upon in this paper. An extensive literature has accumulated on the subject, but the question cannot yet be regarded as settled. However, we know of quite a number of cases in which examination of the tuberculous material has shown that the culture involved behaved atypically. Nature often accomplishes results where the experimenting scientist fails. Atypical tubercle-bacillus growths have often been found in cases of lupus especially. In 18 cases of lupus I isolated atypical tubercle bacilli three times, human bacilli twelve times, and bovine type three times. In reporting on his 23 positive cultures from lupus Kirchner stated that he propagated the human type eleven times and the bovine type twelve times. However, as he himself says, only 13 of these 23 cultures were typical while 10 exhibited atypical properties. Andersen, who worked under Bang in Copenhagen, was likewise able to demonstrate a number of atypical tubercle-bacillus cultures in the lupus cases that he examined.

Particularly valuable, however, in this respect are, as you know, the findings of the English investigators, especially those of Stanley Griffith. Thus, toward the end of 1924 he published interesting investigations regarding *Atypical Tubercle Bacilli in Human and Animal Tuberculosis with Special Reference to Those Occurring in Lupus*. In scrofuloderma, with abscesses in the skin and subcutaneous tissues, Griffith found 8 atypical cultures among 52 cases. In the 140 cases of lupus most of the cultures were atypical with respect to their growth or their pathogenic properties. In 2 cases, in which there was lupus besides internal tuberculosis, and in another 2 cases in which the skin was involved in several places, different foci produced cultures of like behavior as to growth, but of different degrees of virulence. The cultures from the internal foci proved to be more virulent than those generated from the focus of lupus of the same patient. Modification of typical characteristics occurred in both the bovine and human types, as could be positively demonstrated by repeated examinations during the progress of the

disease. It advanced only up to a certain point, after which no further modification of the culture took place. The cause of this progression and its subsequent cessation is not known to us.

Carpenter and Goldberger have recently stated that in cattle also there occur tuberculous diseases of the skin caused by attenuated cultures. These authors were able to produce lupus in calves, and they found that the animals infected experimentally in this artificial manner reacted typically to tuberculin.

CONCLUSIONS

1. Tuberculosis in human adults, especially *phthisis pulmonum*, is in most cases caused by the *typus humanus* of the tubercle bacillus.

2. In a great number of cases however, especially in children, the *typus bovinus* must also be considered as the cause of even severe infections.

3. Occasionally human tuberculosis is caused by strains of tubercle bacilli possessing the biological properties of the avian type.

4. A strict division of the several types is not always possible, as there are atypical intermediate strains.

5. Atypical strains occur very frequently in cases of tuberculosis of the skin (lupus).

6. In a case of *Dermatomyositis recurrens* there have been isolated from the associated pulmonary and intestinal foci cultures of attenuated bovine tubercle bacilli and from the skin a strain with the biological properties of avian bacilli.

7. The possibility is not to be excluded that under certain conditions a transformation of the primary type may take place in the human body.

8. For the definitive decision of the question of type a further study of the atypical strains of tubercle bacilli is especially to be recommended.

REMARKS ON ATYPICAL FORMS OF THE TUBERCLE BACILLUS[1]

ERNST PRIBRAM[2]

Prof. Lydia Rabinowitsch, in her instructive lecture, talked about transitional and atypical forms of the *Bacterium tuberculosis*. It would be of interest to know more of the properties of these cultures. It may be that some of these cultures vary under particular conditions.

Ferrán, the famous dean of Spanish bacteriologists, to whom we owe the first successful vaccination against cholera many years before its general application during the war, assumes that the biology and morphology of the tubercle *Bacterium* can vary very considerably. In his studies over a period of almost forty years he found strains of the typical acid-fast *Bacterium tuberculosis Koch*, which rendered the broth turbid when the broth had been shaken during their growth. Other forms were able to make the broth turbid spontaneously. These types, *delta* and *epsilon*, were acid-fast, as was also the original *Bacterium* of Koch, the *gamma* type of Ferrán. Type *epsilon* sometimes loses its acid-fast characteristics. This is a gradual variation of the properties of the *Bacterium tuberculosis*. In other cultures, but very rarely, Ferrán noticed a sudden loss of both the typical growth and the acid-resistance (*alpha* type of Ferrán). These cultures occasionally became transmuted into forms with Much's granules (*beta* type).

There are other bacteria, which morphologically and biologically are different from the *Bacterium tuberculosis* but which produce a clinical picture similar to that resulting from an infection with acid-fast bacteria, such as the *Bacterium pseudotuberculosis rodentium*. This belongs to the group of bacteria of hemorrhagic septicemia; it is not acid-fast and it is more related to the *Bacterium pestis*. Its other name is therefore *Bacterium pseudopestis* (Albrecht). The clinical picture resembles that

[1] Presented in a *Discussion* of the paper, *The Types of Tubercle Bacilli in Human Tuberculosis*, by Dr. Lydia Rabinowitsch-Kempner, at the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 7, 1926. (See AMERICAN REVIEW OF TUBERCULOSIS, 1927, xv, 225.)

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caused by acid-fast bacteria, such as the formation of nodules in the lungs, but there is no caseation of the tissue. In my studies upon the groups of different bacteria (*B. coli, fluorescens, faecale, alcaligenes, pyocyaneum, septicaemiae haemorrhagicae*, etc.) I could show that there are transitional forms between almost all groups of gram-negative bacteria examined thus far. These transitional forms have morphological and biological qualities which belong to two or more different groups. It may be that these forms may vary in their properties either suddenly or gradually under special conditions. The *Bacterium tuberculosis* itself is a transitional form, not between different forms of bacteria, but between the whole genus *Bacterium* and the genus *Hyphomyces* (*fungi imperfecti*). The genus *Hyphomyces* sometimes varies quite extensively. I described, for instance, a mould, isolated from a lac tree by Mahdi Hassan in Bangalore, which not only changed into two other different forms of moulds, but the conidia of which were three or even four different types of yeasts,—*Saccharomyces apicatus, Zygosaccharomyces, Schizosaccharomyces*, and *Oidium*. All these forms could be obtained from one cell, the *Oidium* cell of this microörganism (isolated by Burri's method).

Another mould, the *Actinomyces*, is very variable also. Some strains, but not all, vary from the typical mould to bacteria or bacilli; others split off cocci. As we know, the *Bacterium tuberculosis* is closely related to the *Actinomyces*. According to the nomenclature of Lehmann and Neumann, both belong to the group *Mycobacterium*. The characteristics of this group are ramification, formation of hyphae and slow growth. It may be, I believe, that the caseation of the tissues also is caused by the mould character of this group.

It may be difficult to find those very cultures which are able to change their morphological and biological characters, and this may be the reason why Ferrán's discoveries could not be repeated even by himself with other cultures of the *Bacterium tuberculosis*. But there are some other authors who have arrived at similar findings. Ferrán's work is of importance for tuberculosis therapy. According to his theory there are two qualities of the *Bacterium tuberculosis:* one, the toxic quality, producing fever and consumption; the other, the quality giving rise to the relatively harmless tubercle-formation. He found that, upon losing its acid-resistance and its typical growth, the toxicity of the culture increased. His *Vacuna antialpha* contains an antitoxin against the toxic component of the transmuted form of the *Bacterium tuberculosis*.

THE VARIABILITY OF LOCALIZATION OF TUBERCULOSIS IN THE ORGANS OF DIFFERENT ANIMALS[1]

IV. THE CELLULAR FACTOR IN THE SUSCEPTIBILITY OF THE VARIOUS ORGANS

H. J. CORPER AND MAX B. LURIE

In the three previous papers of this series (1) (2) (3) it was observed, first, that the distribution of tubercle bacilli to the various organs after intravenous injection in the different species studied (guinea pig, rabbit, dog and monkey) could not alone account for the resulting tuberculous involvement of the organs; and, second, that the growth of the bacilli in the different organs of each species, as determined by the oxygen tension available for the cells in which the tubercle bacilli are found, could not alone account for the tuberculous involvement; nor would these two factors taken together entirely explain the variability of the tuberculosis found in the different organs. Therefore, still other factors must be sought in order to determine further unknown factors of the mechanism of the disease, its spread in the body, and the forces involved in the body's protection against it.

Thus far the studies have been concerned with the tubercle bacillus,—its localization and growth within the body. That the cells and tissues of the animal organism react to the injurious effects of the presence and growth of tubercle bacilli is too self-evident to require lengthy exposition, but the process of determining the importance of this bodily force, when the tubercle bacilli are living, is admittedly complicated. Since, however, dead tubercle bacilli, when introduced into the body, do cause the formation of tubercle, and since also the distribution of tubercle bacilli to the different organs after intravenous injection is known, it seemed advisable to study, quantitatively, tubercle-formation in the different organs of the several species of animals after the intravenous injection of heat-killed tubercle bacilli alone and of these with carbon (india ink). It was hoped thus to be able to throw further light on organic tuberculosis, since in this case the tubercle bacilli, one prime

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factor in tuberculosis, could be kept constant while the other variable, the body-cell, was being studied.

Different amounts of dead (heat-killed) virulent human and bovine tubercle bacilli were injected intravenously into the four different species of animals, and the resulting pathological changes were studied microscopically. In order to correlate better the tuberculous changes resulting from the injection of dead bacilli and those resulting from living bacilli, a number of animals from each species were given intravenous injections of large amounts of an avirulent strain of living bacilli, and the pathological changes produced were studied microscopically.

For the injections definite amounts of bacilli were weighed, and these were autoclaved for two hours at 15 to 20 pounds steam-pressure, after which they were ground up with the aid of a few drops of sterile soap solution and suspended in salt solution. These suspensions were injected intravenously; and about one month after injection the animals were killed by exposure to illuminating gas and careful autopsies were made. The tissues for examination were fixed in Zenker's solution, embedded in paraffine, sectioned, and stained with hematoxylin and eosin, as well as for bacilli. The numbers and sizes of the tubercles seen in 50 high-power fields, using a no. 5 ocular and 4 mm. objective, were recorded and tabulated.

THE CELLULAR REACTION OF THE ORGANS OF RABBITS TO DEAD VIRULENT BOVINE TUBERCLE BACILLI

The simultaneous injection of dead bovine tubercle bacilli and india ink intravenously demonstrates clearly that the cells which react with the formation of tubercle to living bacilli are identical to those that react to dead bacilli; the epithelioid cells of all of the tubercles in the different organs are heavily laden with carbon particles, and the carbon is more dense than if the animal had received living bacilli, since in the latter case the repeated division of the epithelioid cells gradually diminishes their carbon load.

Tubercles in the lung originate from the histiocytic elements beneath the endothelium of the blood-vessels, occasionally causing a gradual obliteration of the lumen. The adventitial cells surrounding the blood-vessels also play a rôle in tubercle-formation, but the most frequent origin for the tubercle is from the histiocytic (?) elements of the alveolar septa. The resulting tubercles are essentially of the productive type. With small amounts of dead bacilli (150 mgm.) the reaction is apparently

a histiocytic hyperplasia of the elements about the blood-vessels, bronchi and alveolar septa. The direct transformation of these hyperplastic cells into typical epithelioid cells can often be traced. With larger doses of dead bacilli (300 mgm.) distinct tubercle-formation occurs in typical cases, consisting of a central core of epithelioid cells, which possess rounded or oval nuclei and a large amount of amoebic eosinophilic cytoplasm, and a peripheral layer of cells which casually resemble lymphocytes but on careful examination differ distinctly from them. Whether they are hyperplastic histiocytic elements was not decided; still, with larger amounts of dead tubercle bacilli (600 mgm.) there occurs a mixed reaction of both exudative and productive character, at times the one and again the other predominating. In exudative cases the alveoli are filled with closely packed cells resembling the monocyte of Sabin, Doan and Cunningham (4). These exudative types of cells often form large giant cells. Tubercles in the lung tend to attain a larger size than in any of the other organs of the body of the same animal.

In the rabbit's liver, after intravenous injection of dead or living tubercle bacilli, the Kupffer cell is the most prominent in the formation of the tubercle. The histiocytic elements of the portal canals appear to play a secondary rôle in this. The tubercles after the injection of dead bacilli to a great extent consist of single Langhans giant cells. Pigment deposits were not apparent in these cells. The liver tubercles are the smallest seen in any of the organs in which tubercle-formation occurs. The arrangement of tubercles due to dead bacilli is similar to that caused by living bacilli, for the tubercles occur mainly at the periphery of the lobule in close proximity to the portal canals.

In the spleen, after the intravenous injection of dead bacilli, the tubercles are composed primarily of large epithelioid cells, and often of giant cells containing a large amount of brown blood pigment as well as altered erythrocytes. The tubercles are found primarily in the pulp. The tubercles in the corpuscles, when present, contain little if any blood pigment. This would be in favor of the view that the macrophage of the spleen is important in the origin of tubercle in this organ. There is no fundamental difference between the structure of the tubercle caused by living or by dead tubercle bacilli in the spleen. The hemoglobin pigment deposited in the epithelioid cells of the splenic tubercles is heavier after the injection of dead bacilli than after living bacilli, and thus resembles carbon. This difference is probably due to a greater division of the rapidly growing epithelioid cells occasioned by living bacilli as compared

to the limited division of the epithelioid cells caused by dead bacilli. The size of tubercles due to dead tubercle bacilli in the spleen closely approximates that in the lung, though they are not quite as large.

The kidney of the rabbit rarely develops tubercle after the intravenous injection of dead tubercle bacilli. In the bone-marrow there is no appreciable qualitative difference between tubercle-formation with living or dead bacilli. Aside from an increased tendency to an exudative tuberculous pneumonia, as a result of the larger amounts of dead tubercle bacilli, the size of the individual tubercles occurring in each organ is not definitely increased, but the number of individual tubercles is greater in a given area as the dose of tubercle bacilli increases. The rabbit will tolerate a fairly large amount of dead bacilli (150 mgm.) intravenously without tubercle-formation. The tubercles in the different organs, after intravenous injections of dead bacilli, range, according to size: the lung, the spleen (the pulmonary tubercles are only slightly larger), the bone-marrow and the liver.

According to the number of tubercles developed in a given area, the organic sequence is as follows: the spleen, with the liver closely following, and the lung. This, in general, parallels the distribution of carbon to these organs.

THE CELLULAR REACTION OF THE ORGANS OF RABBITS TO DEAD VIRULENT HUMAN TUBERCLE BACILLI

The cytological reaction to killed virulent human bacilli in the different organs of the rabbit is not different in kind from that occurring with dead virulent bovine bacilli. All the characteristic findings noted with dead bovine bacilli apply equally well as to dead human bacilli. The number of tubercles occurring in each organ tends to diminish with the amount of dead bacilli introduced intravenously. The average number of tubercles occurring in the lungs of rabbits receiving 600 mgm. of dead human bacilli is 1.1 per high-power field, while with 150 mgm. only 0.5 tubercles were found. In the liver 2.8 tubercles occurred after 600 mgm., while after 150 mgm. 2.1 tubercles were found; after 600 mgm. 4.4 tubercles were found in the spleen, while with 150 mgm. 3.5 tubercles were observed.

The average number and size of tubercles found after dead human bacilli for all the amounts summarized resulted as follows:

	LUNG	LIVER	SPLEEN	KIDNEY	BONE-MARROW
Number per high-power field	1.0	2.3	4.2	0	1.2
Size in micra	97	50	92		64

It is noted that the foregoing ratio of the number of tubercles occurring in the different organs parallels the distribution of carbon to these organs. The lung develops the fewest tubercles, the bone-marrow next, then the liver, and finally the spleen the largest number of tubercles. The evidence tends further to verify the similarity of distribution of tubercle bacilli and inanimate particulate matter. The size of the tubercles agrees well with the findings after the injection of dead virulent bovine tubercle bacilli; for the pulmonary tubercles tend to be larger than those in any other organ, the splenic tubercles are a close second, then come tubercles in the bone-marrow, and finally the hepatic tubercles are smallest.

The only difference between the cellular reaction (as measured by tubercle-formation) to dead human and dead bovine tubercle bacilli is quantitative, the number and size of the tubercles resulting from dead human bacilli being fewer and smaller than those from dead bovine bacilli. This can be explained only as being due to a difference in the chemical composition of the two microörganisms. Since the most important difference in chemical composition between bovine and human bacilli is the greater lipoid content of the former, it seems reasonable to conclude that one of the most important factors in tubercle-formation is the lipoid content of the tubercle bacillus. Since there is a tendency for the number of tubercles to diminish with the decrease in the amount of dead bacilli injected, and since with small amounts of dead tubercle bacilli no appreciable tubercle develops, the development of tubercle is an evidence of the presence, within the cells which phagocytose the bacilli, of undestroyed material, probably of lipoid nature. This undestroyed material of the tubercle bacillus stimulates the cell to form epithelioid and giant cells. The size of the tubercle in the different organs, therefore, is inversely proportional to the digestive or destructive power of these cells for the chemical constituents of the tubercle bacilli, and the greater the digestive or destructive power of a given cell for dead tubercle bacilli the smaller will be the resultant tubercle formed by this type of cell.

One factor in the marked relative resistance of the liver of the rabbit to infection with living tubercle bacilli is the ability of the Kupffer cells to destroy the chemical components of the tubercle bacillus; but the cellular reaction alone cannot explain the organic susceptibility of the rabbit to tuberculosis, because the cellular reaction of the rabbit's lung closely approximates that of the spleen in this animal after the intra-

venous injection of living bacilli, yet there is a strikingly greater difference of resulting tubercles than can possibly be accounted for by the difference in the destructive power for tubercle bacilli of the cells giving rise to the tubercles in them.

The greater amount of tuberculosis developed in response to the injection of dead virulent bovine bacilli as compared to dead virulent human bacilli may involve a factor in the greater susceptibility of the rabbit to bovine infection.

TABLE 1

Tubercle formation in the organs of rabbits after the intravenous injection of dead virulent human and bovine tubercle bacilli. Table of averages

AMOUNTS		LUNG		LIVER		SPLEEN		KIDNEY		BONE MARROW	
		Bovine virulent	Gluckson	Bovine virulent	Gluckson	Bovine virulent	Gluckson	Bovine virulent	Gluckson	Bovine virulent	Gluckson
600 mgm.*	No. phpf.†	2.5	1.1	4.5	2.8	4.1	4.4	0	0	0.8	0.7
	Size in U.†	118	89	55	57	112	114			58	63
300 mgm. +1.‡	No. phpf.	3.6	0	6.5	0	5.7	0	0.3	0	1.6	0
	Size in U.	111	0	56		107		34		88	
300 mgm.	No. phpf.	1.0	1.6	1.4	2.1	4.1	4.7	0	0	2.0	2.3
	Size in U.	114	105	62	51	94	93			68	72
150 mgm.	No. phpf.	+	0.5	0	2.1	+	3.5	0	0	0	0.7
	Size in U.		98		41		69				59
Average of all doses	No. phpf.	2.3	1.0	4.1	2.3	4.6	4.2	0	0	1.1	1.2
	Size in U.	114	97	57	50	107	92			71	64

* The average figures recorded in this table were obtained from the examination of at least four to six rabbits given the human or bovine strain of bacilli intravenously. The animals were examined usually 25 to 43 days after injection, the majority being examined at about 30 days.

† The heading *No. phpf.* indicates the number of tubercles per high-power field using a no. 5 ocular and a 4-mm. objective, and averaging the results of the examination of 50 fields. Under the column *size in U* the figure gives the average size in micra of the tubercles.

‡ These rabbits were given intravenous injections of 1 cc. of Higgins *Waterproof* india ink per pound body weight coincidently with the 300 mgm. of dead tubercle bacilli.

TUBERCLE-FORMATION FOLLOWING THE INTRAVENOUS INJECTION OF LIVING AVIRULENT HUMAN TUBERCLE BACILLI

There is no fundamental difference between the reaction following large intravenous injections (150 mgm.) of living avirulent human bacilli

as compared with dead bacilli. The sections of the lung, liver, spleen, kidneys and bone-marrow from four rabbits, given 150 mgm. of living avirulent human bacilli, showed essentially the same microscopic pictures as those after the injection of dead bacilli. The relative size of the tubercles produced in the different organs follows closely that seen with dead bacilli. The average figures for these four rabbits in the lung were 3.0 tubercles per high-power field and their average size was 136 micra, in the liver 2.0 tubercles of 64 micra, in the spleen 3.0 tubercles of 109 micra, in the bone-marrow 1.7 tubercles of 97 micra, while the kidney revealed no tubercles in these animals. Pulmonary tubercle is the largest; splenic, bone-marrow and liver tubercle follow in sequence, the latter being smallest. The number of tubercles, however, does not follow the ratio noted for the distribution of the carbon and of dead bacilli, in that the lung and liver now have changed positions, the lung containing more tubercles than the liver. No doubt this difference is due again to the greater ability of the living bacilli to grow in the lung as compared to the liver, as a result of the greater oxygen head-pressure in the lung than in the liver sinusoids.

THE CELLULAR REACTION OF THE ORGANS OF DOGS TO DEAD VIRULENT HUMAN AND BOVINE TUBERCLE BACILLI

After the intravenous injection of large amounts of dead human or bovine tubercle bacilli, there was a marked tendency for the development of an acute exudative pneumonia, the nature of which varied somewhat with the individual animal. In many cases it was a frank pneumonia, with an exudation of polymorphonuclear cells, red blood corpuscles, fibrin, and desquamation of the cells lining the alveolar walls. In some cases desquamation predominated while the polymorphonuclear exudate was not so pronounced. The desquamation of alveolar epithelium leaves markedly congested endothelial tubes, and the alveolar spaces are filled with large phagocytic cells resembling mobilized reticulo-endothelial cells, which do not tend to become collected into nodules or to form giant cells, as is seen in the exudative tuberculosis in the rabbit. This pulmonary process in the dog can hardly be interpreted as a tuberculous reaction.

The liver in these cases shows a marked fatty degeneration of the parenchyma, extending from the central vein to the periphery of the liver lobule; and commonly only the cells in immediate proximity to the portal canals are intact. The spleen shows the macrophages excessively

laden with the products of red-blood-cell disintegration. Occasionally there occurs a destruction of red blood cells *en masse*, when the cells are converted into hyaline staining eosinophilic patches. Similar excessive deposits of hemoglobin pigment are seen in the bone-marrow, and one animal showed the Kupffer cells laden with this pigment.

It is noteworthy that in these animals, having received about 1000 mgm. of dead tubercle bacilli, there was a complete absence of tubercle-formation in any of the organs. This type of reaction appears to be antagonistic to tubercle-formation. In dog *D9*, in which there occurred only a slight pneumonic process, a few small tubercles formed in the liver. It is conceivable in these cases that the pneumonic process in the lungs may have masked any tubercle-formation, but this cannot be said to be the case with the other organs.

After the intravenous injection of moderate doses of dead tubercle bacilli the organs of the dog react in a characteristic manner. The pulmonary tubercles originate mainly from the alveolar walls. If dead tubercle bacilli and carbon particles are injected simultaneously, the epithelioid cells of the tubercles in the different organs contain carbon particles and, in distinction to the rabbit, a stimulation of the pericyte or subendothelial histiocyte, with vascular obliteration, is not seen in the dog. The adventitial cells of blood-vessels and of bronchi, however, respond actively to the injection of dead tubercle bacilli, thus resembling the reaction to living bacilli. The character of the tubercle formed in the lungs of dogs in response to living or dead bacilli is essentially identical, and consists of typical epithelioid cells closely packed together and assuming a more or less spindle-shaped form. In cases of spontaneous anthracosis many of the epithelioid cells of the tubercles produced by dead bacilli contain carbon particles, indicating that the histiocytic elements in the lung, which had previously picked up carbon, can phagocytose both dead and living bacilli, become transformed into epithelioid cells and form part of the tubercle. The ratio between the number of tubercles in the lung and liver would indicate that many phagocytosed dead tubercle bacilli have been destroyed without their having caused tubercle-formation. In the rabbit the number of tubercles developed in each organ paralleled fairly well the deposition of carbon. But in the dog neither the lung nor the spleen show a parallelism between tubercle-formation and carbon deposition. It would appear, therefore, that the phagocytic cells of the lung, and especially of the spleen, of the dog possess the power to destroy or digest tubercle bacilli

in considerable degree, so that tubercle-formation is correspondingly depressed. In contrast to the findings in the rabbit, tubercle in the dog's lung is decidedly smaller than that in the liver, and tubercle in the liver after the intravenous injection of dead tubercle bacilli is larger than that occurring in the spleen, kidney, lung or bone-marrow.

Microscopically, the tubercles produced with dead bacilli are essentially the same as those produced by living bacilli in the different organs. The characteristic tubercle in the liver consists of many loosely arranged epithelioid cells with numerous cytoplasmic processes, intermingled with some polymorphonuclear cells, and often enveloping red blood cells from the sinusoids in which the tubercles originate. The tubercles are largest, and tend to fuse, to form elongated or ovoid masses, often in chain-form, at the periphery of the liver lobule. The tubercles in the centre of the liver lobule tend to be more or less spherical and are smaller than those at the periphery. Localization is related to the deposition of the bacilli, as is indicated by the distribution of the carbon. To some extent the adventitial cells of the blood-vessels partake in the formation of tubercle in the liver, but by far the most prominent cell is the Kupffer cell.

The number of tubercles in the spleen, after the intravenous injection of dead bacilli, closely corresponds to the number occurring in the lung, but their size is much smaller. The epithelioid cells often contain hemoglobin pigment and are not in compact association. In the dog it may appear as though carbon did not serve as an index to the distribution of bacilli, since the carbon is localized in the spleen not only more than in the lung but even more than in the liver, and yet the number of tubercles found in the spleen after the intravenous injection of dead tubercle bacilli is no greater than occurs in the lung, while in the liver there occur about five times as many tubercles. There is, however, no reason to suppose that the carbon deposition in the spleen of the dog is not an index of the deposition of the bacilli, since all the facts upon which is based the identity of the distribution of carbon and tubercle bacilli to the different organs also hold in the dog. Thus the epithelioid cells are laden with carbon particles after the simultaneous introduction of tubercle bacilli and carbon, and only those organs become involved in which there is found deposited an appreciable amount of carbon. There remains only one explanation for the slight splenic involvement in the dog, and that is that the cells in the spleen which phagocytose tubercle bacilli have a marked ability to destroy the bacilli, so that only when large amounts are phagocytosed is the destruction incomplete and tubercles can form.

In the dog the importance of the cellular reaction in the development of tuberculosis following the injection of living bacilli is well illustrated. The extensive involvement of the liver is due to the limited power of the Kupffer cells to destroy the bacilli, and the striking absence of tuberculosis in the spleen of the dog, except when large amounts of tubercle

TABLE 2

Tubercle formation in the organs of dogs after the intravenous injection of dead virulent human and bovine tubercle bacilli. Table of averages

AMOUNT		LUNG		LIVER		SPLEEN		BONE MARROW	
		Bovine virulent‡	Gluckson	Bovine virulent	Gluckson	Bovine virulent	Gluckson	Bovine virulent	Gluckson
800 mgm. + 1.1.*	No. phpf.†	1.3		4.1		1.1		0.8	
	Size in U.†	124		173		165		86	
1000 mgm.	No. phpf.		1.0		3.6		0.7		0.3
	Size in U.		111		156		80		60
500 mgm.	No. phpf.	1.0	0.4	3.9	3.9	0.5	0.4	+	0.3
	Size in U.	107	88	125	135	66	74		56
200 mgm.	No. phpf.	0.3	0.3	3.2	4.3	0.6	0.5	0.6	
	Size in U.	93	77	149	173	64	68	47	
Table of averages	No. phpf.	0.7	0.7	3.2	3.5	0.7	0.6	0.5	0.3
	Size in U.	104	100	142	150	97	75	68	58

* These dogs were given intravenous injections of 1 cc. of Higgins *Waterproof* india ink per pound body weight coincidently with the injection of the 800 mgm. of dead tubercle bacilli.

† The heading *No. phpf.* indicates the number of tubercles per high-power field using a no. 5 ocular and a 4-mm. objective and averaging the results of the examination of 50 fields. Under the column *size in U* the figure gives the average size in micra of the tubercles.

‡ The average figures recorded in this table were obtained from the examination of from 2 to 10 dogs in the individual series and with the different strains of human or bovine tubercle bacilli. The animals were examined usually 25 to 35 days after the injection, the majority being examined on the thirtieth day.

Tubercle was only rarely found in the kidney after the injection of dead bacilli and this organ is therefore not recorded.

bacilli have been injected, is the result of the ability of the histiocytic elements of the spleen to effectually destroy the tubercle bacilli.

These observations make it seem unlikely that the predominant rôle in epithelioid-cell formation is played by a circulating blood cell or by a single type of cell, for if this were true it would hardly be conceivable that the same leucocyte or monocyte should have one physiological function

in the spleen, with a remarkable property of destroying tubercle bacilli, and the same cell when located in the liver should at once to a great extent lose this power.

Tubercles in the bone-marrow are fewer in number than those in the spleen and they are smaller. In the dog, also, the number and, to a less extent, the size of the individual tubercles, occurring as a result of the injection of larger amounts of dead bacilli, are greater than result from smaller injections of dead bacilli. In the dog there was no marked difference in the amount of tuberculosis resulting from the intravenous injection of dead bovine as compared with dead human bacilli, and this circumstance is to be correlated with the fact that there exists in the dog no marked difference in susceptibility to living virulent human and virulent bovine tubercle bacilli.

A comparison of the nature of the response in the organs of the dog to dead tubercle bacilli and to living avirulent human and bovine bacilli reveals no fundamental difference. In both cases the tubercles in the liver are the largest, the tubercles in the lung following in sequence, then the splenic tubercles being next in size, while the tubercles of the bone-marrow are the smallest; and the tubercles in the liver are the most numerous, while those in the bone-marrow are the fewest. After the injection of dead bacilli the tubercles in the lung are equal in number to those in the spleen, while after the injection of living avirulent bacilli the tubercles in the spleen distinctly outnumber those in the lung.

The average figures obtained in the case of three dogs, 33 days after an intravenous injection of 300 mgm. of living avirulent human tubercle bacilli, showed 0.3 tubercle 156 micra in size in the lung, 3.6 tubercles 203 micra in size in the liver, 1.9 tubercles 138 micra in size in the spleen, and 1.7 tubercles 119 micra in size in the bone-marrow, while the kidney was practically negative.

THE CELLULAR REACTION IN THE ORGANS OF THE GUINEA PIG AFTER THE INTRAVENOUS INJECTION OF DEAD VIRULENT HUMAN AND BOVINE TUBERCLE BACILLI

The outstanding effect in the lung of the guinea pig of the intravenous injection of heat-killed human or bovine tubercle bacilli is the production of marked perivascular reaction. The smaller vessels are surrounded by a ring of closely packed cells with deeply stained nuclei and containing a slight amount of pale cytoplasm. Commonly the ring is composed of only two or three layers of cells, but in many cases they may become

quite large, and on casual examination appear to be lymph follicles in the substance of the lung tissue. These nodules are not ordinary hyperplastic lymph follicles since there is usually a blood-vessel passing through the centre. Some of the cells of these nodules resemble typical lymphocytes, being small cells with round, deeply stained nuclei and a

TABLE 3

Tubercle formation in the organs of the guinea pig after the intravenous injection of dead virulent human and bovine tubercle bacilli. Table of averages

AMOUNT		LUNG		LIVER		SPLEEN	
		Bovine virulent‡	Gluckson	Bovine virulent	Gluckson	Bovine virulent	Gluckson
50 mgm.	No. phpf.†	0.2	0.2	1.2	1.5	2.0	1.4
	Size in U.†	77	62	67	68	97	115
50 mgm. + 1.1.*	No. phpf.			1.5	1.5	1.5	1.8
	Size in U.			124	86	120	135
100 mgm.	No. phpf.		0.8	1.3	0.8	1.8	0.3
	Size in U.		77	68	52	106	66
150 mgm.	No. phpf.	0.3	0.9	3.3	2.3	3.9	3.1
	Size in U.	85	72	90	94	121	142
Average of all doses	No. phpf.	0.4	0.6	1.8	1.5	2.4	1.7
	Size in U.	82	75	82	74	108	111

* These guinea pigs were given intravenously injections of 5 cc. of a 1:5 dilution of Higgins *Waterproof* india ink coincidently with the 50 mgm. of dead tubercle bacilli.

† The heading *No. phpf.* indicates the number of tubercles per high-power field using a no. 5 ocular and a 4-mm. objective and averaging the results of the examination of 50 fields. Under the column *size in U* the figure gives the average size in micra of the tubercles.

‡ The average figures recorded in this table were obtained from the examination of about 4 guinea pigs in each individual series and under the different strains of human or bovine tubercle bacilli. The animals were examined 30 to 35 days after the injection of the dead bacilli. The kidneys and bone marrow were rarely affected after the injection of dead bacilli, so that these organs are not included in the tabulation of the guinea pigs.

sparse rim of cytoplasm, while others have larger vesicular nuclei with a larger amount of clear basophilic cytoplasm. Interspersed among these cells are found elongated cells with long spindle-shaped vesicular nuclei, usually bent in *S* shape with fibrillar cytoplasm. Occasionally, typical lymphocytes are seen in the lumen of the vessel close to the endothelial wall, and occasionally these could be seen through the endothelial lining

of the blood-vessel. An infiltration of the alveolar walls with these cells also occurs, and their apparent direct transformation into typical epithelioid cells is common in the sections of the lung of the guinea pig. The nature of the perivascular reaction, whether a migration of lymphocytes (?), occasioned by the presence of the dead tubercle bacilli, which later become phagocytic cells and transformed into typical epithelioid cells, or whether of another type of cell was not determined. In any case this reaction differs from that seen in the rabbit and dog at least in degree if not in kind.

In estimating the number and size of tubercles present in the lungs of the guinea pig, these nodules were not considered tubercles unless they had progressed to the stage of transformation into typical tubercles with characteristic epithelioid cells. In recording the average (table 3) only characteristic tubercles were considered, and the nodules occurring in the guinea pigs' lungs were not considered as tubercles.

The tubercles in the guinea pig's lung after intravenous injection of dead tubercle bacilli originate from the perivascular cells and perhaps also from similar cells in the alveolar walls.

While there was found a decided individual variation among the guinea pigs, there occurred, as in the dog and rabbit, an increase in the number of tubercles with increasing amounts of dead bacilli injected and a less marked increase in the size of the tubercles. Simultaneous injection of dead tubercle bacilli and india ink resulted in the tubercles in the lung being laden with carbon, again indicating the identity of the cells phagocyting the tubercle bacilli and the carbon particles. Even though there exists a decided variation in the size of the pulmonary tubercles in the individual animals, the size of the tubercles in the lung and in the liver tend to be about the same in the guinea pig after the injection of either dead human or dead bovine tubercle bacilli. As in the case of the rabbit and dog, the number of tubercles occurring in the lung after the intravenous injection of dead bacilli is smaller than in the other organs. There was no appreciable difference in the reaction in the lung to dead virulent human or dead virulent bovine bacilli. Slightly larger tubercles developed in response to dead bovine than to dead human bacilli.

In the liver of the guinea pig, after the intravenous injection of dead tubercle bacilli, the most prominent cell of origin of the tubercle was the Kupffer cell. Tubercles of characteristic epithelioid-cell structure formed in the sinusoids, and Langhans giant cells were common. In

some cases the arrangement of the tubercles was around the periphery of the lobule and in conjunction with the portal canals, while in other cases they were clustered about the sublobular veins. Occasionally there occurred a perivascular reaction about the portal vessels, which resembled the same reaction in the lung, and the cells were sometimes seen in the stages of transformation into epithelioid cells. The simultaneous injection of india ink and tubercle bacilli intravenously resulted in the epithelioid cells of the tubercles being laden with carbon particles.

The effect of dosage of bacilli is clearly evident in the liver of the guinea pig. With 50 mgm. of dead virulent bovine bacilli, the average number of tubercles per high power field in four animals was 1.2, and the average size was 67 micra, while with 150 mgm. the number was 3.3 per high power field and the size 90 micra. The primary effect of increase in dosage was an increase in the number of tubercles with a less evident increase in their size.

In considering the significance of these findings, it is evident that the body might dispose of the bacilli in one of three ways when the amounts of bacilli are increased: (1) Either the number of cells phagocytosing bacilli is the same as when smaller amounts have been injected, but each individual cell becomes more heavily laden. (2) With increasing amounts of bacilli more cells become laden with them, while the number of bacilli deposited in each cell remains the same. (3) Both the number of cells serving as depositories for the bacilli and the amount deposited in each cell might increase coincidently. Since, with increasing amounts of bacilli injected there is an increase in both the number and size of the tubercles, it follows that the third possibility holds; but since the effect on the number of tubercles is more pronounced than on their size, it is reasonable to conceive that while the individual cells are slightly more heavily laden, more cells phagocytose the bacilli.

After the intravenous injection of small amounts of dead tubercle bacilli the tubercles in the liver become more or less spherical, while after large amounts (150 mgm. human or bovine bacilli) they are angular, as is also the case in the liver of guinea pigs injected with living bacilli. In an occasional animal necrosis is seen in the tubercles in the liver after the injection of dead bacilli.

The ratio between the number of tubercles occurring in the lung and liver after the injection of dead bacilli is about the same as the relative deposition of carbon, the tubercles occurring in the liver being more numerous than in the lung. No appreciable difference in the size of the tubercles occurring in these two organs was noted.

The spleen in the guinea pig reacts to the intravenous injection of dead tubercle bacilli by the formation of typical tubercles and, when carbon is injected simultaneously with the dead bacilli, the epithelioid cells of the tubercles are laden with carbon particles. The tubercles occur predominantly in the pulp, only a few occurring in the corpuscles. Giant-cell formation is pronounced in the tubercles of the spleen. As occurs in the case of the rabbit and dog, the epithelioid cells frequently contain altered red blood corpuscles and hemoglobin pigment, indicating the possible identity of the cell which phagocytoses the altered red blood cells and the dead tubercle bacilli. With increasing amounts of tubercle bacilli injected, there occur an increase in the number of tubercles developed and a less pronounced increase in their size, as in the liver. After the intravenous injection of large amounts (150 mgm.) of dead tubercle bacilli, the pulp is almost completely transformed into tuberculous tissue. In occasional cases a transformation *en masse* of the endothelial cells lining the blood sinuses into epithelioid cells is noted, and there then occurs marked congestion of these sinuses, and the microscopic picture resembles that seen in guinea pigs infected with virulent living bacilli. The difference is only in the severity of the process, and not in its fundamental nature. The splenic tubercles resulting from the intravenous injection of dead tubercle bacilli are invariably larger than the tubercles occurring in any of the other organs. There tends to be present a greater number of tubercles than in the other organs, but this is not as striking as the greater size of the tubercles.

The number of tubercles occurring in the spleen of the guinea pig, compared to those in the other organs, parallels fairly well the distribution of carbon.

The significance of the size of the tubercle in the guinea pig is susceptible of the same interpretation as that given in the case of dog and rabbit, the size of the tubercle being the index to the amount of undestroyed tubercle bacilli. Dead tubercle bacilli in the tissues act as an irritating foreign body, causing the phagocytic cells containing them to become transformed into typical epithelioid cells. The bacilli cause these cells to divide, and their burden of tubercle bacilli is distributed among the daughter cells. Whether the daughter cells will continue to divide and form a larger or a smaller tubercle depends upon the fate of the tubercle bacilli. If the cell can change these, so that no irritating material is left behind, the multiplication of the epithelioid cells ceases, and small tubercles or single giant cells form, as occurs in the liver of the

rabbit, to destroy the bacilli. If, however, the physiological power of the cell is limited, division must continue, and hence the resulting tubercle is large. It would thus seem that the size of the tubercle is an index of the digestive or destructive power for tubercle bacilli of the cell of origin of the tubercle in the various organs.

However, the size of the tubercle is an index not only of the destructive power of the cell for dead bacilli but also of the original amount of bacilli phagocytosed by the cells, since of two cells with equal ability to destroy tubercle bacilli the one which is laden with ten times as many bacilli as the other will of necessity give rise to a larger tubercle.

It was established in the studies on carbon that, weight for weight, more foreign particles are deposited in the spleen following intravenous injection than in any other organ of the body. This occurs conceivably in one of three ways: (1) Either more cells in a given amount of tissue store carbon than in the same amount of tissue or lung; (2) the same number of cells in the spleen each store more carbon than do the same number in the liver; or (3) more cells in a given amount of tissue store more carbon each than in the lung or liver. Since an increase in dosage of bacilli, irrespective of the organ, affects the number of tubercles rather than their size, this would indicate that a certain number of cells tend to become almost completely saturated, even after small injections; and additional quantities introduced only slightly increase the load of foreign material phagocytosed by each cell, and the main effect is that a larger number of cells take up the bacilli with larger doses. While it is admittedly impossible to determine definitely whether the individual Kupffer cells of the liver take up more carbon particles after the intravenous injection of india ink than the phagocytic cells of the spleen, no evident difference between them could be noted. The number of phagocytic cells in the spleen is admittedly greater than in the liver; and, since in the spleen, as in the other organs, the main effect of increase in dosage is not an increase in the size but an increase in the number of tubercles after the injection of dead bacilli, it follows that a certain number of phagocytic splenic cells tend to become saturated, following the introduction of particulate material into the circulation. Since the same thing is true in the liver of the guinea pig, it follows that, after the injection of particulate matter, a certain number of Kupffer cells tend to become nearly loaded, and, therefore, the greater amount of carbon or tubercle bacilli which is deposited in the spleen, as compared to that deposited in the liver, must be among a greater number of cells in the

spleen. The larger number of original depositories for dead tubercle bacilli in the spleen accounts for the larger number of tubercles developed in the spleen; but, since each phagocytic cell tends to become saturated with the particulate material, there is no reason to suppose that the individual depositories in the spleen contain more bacilli than the individual depositories in the liver, although the number of depositories in the spleen is greater than in the liver. If the individual Kupffer cells in the liver do not contain more carbon particles or more bacilli than the phagocytic cells of the spleen, it is obvious that the larger size of the

TABLE 4

Relative amount of tuberculosis occurring in the organs of the different species of animals as a result of the intravenous injection of dead human and bovine tubercle bacilli

	RABBIT		GUINEA PIG		DOG	
	Bovine virulent	Gluckson	Bovine virulent	Gluckson	Bovine virulent	Gluckson
Lung	262.2*	97	32.8	45	72.8	70
Liver	233.7	115	147.6	111	454.4	525
Spleen	492.2	386.4	259.2	188.7	67.9	45
Bone-morrow	78.1	76.8			34	17.4
Total	1066.2	675.2	439.6	344.7	629.1	657.4
Ratio in per cent of quantity of tuberculosis comparing Gluckson and Bovine		0.63†		0.78		1.04

* The figures in this table are arrived at by multiplying in the case of each organ of each animal the average figure for the size in micra of the tubercle by the average figure for the number of tubercles of the entire series of animals.

† The figure in the last line is obtained by dividing the sum of all the figures or the figure in line *Total* for the *Gluckson* strain by the figure obtained for the *Bovine* strain under each animal species.

tubercles in the spleen of the guinea pig is due to a more limited destructive power on the tubercle bacillus of the phagocytic cells of the spleen, as compared to the Kupffer cells of the liver or the cells of origin of the tubercle in the lung.

There appears to be objections to these deductions, in that the phagocytic splenic cells appear to be more numerous in a given area than the Kupffer cells of the liver, and the larger size of the tubercles in the spleen of the guinea pig is due to a fusion of several foci into one. But, if this is so, why are the tubercles in the liver more numerous but of the same

dimensions as those in the lung when the deposition of bacilli in the liver is much greater?

A consideration of the guinea pig alone is perhaps not sufficiently convincing that the size of the tubercle is an index of the destructive power of the cell for the tubercle bacillus. But, if this is not the case, how can the small number of tubercles and their small size in the dog's spleen be explained, and why are the tubercles in the rabbit's liver so small and yet so numerous after the injection of dead bacilli? Why are the tubercles in the liver of the dog so large and so numerous after the intravenous injection of dead bacilli, while the spleen, in which are deposited more tubercle bacilli, contains a very small number of tubercles of very small size? Why does tubercle in the rabbit's lung, after the injection of dead tubercle bacilli, attain a larger size than the tubercle in any other organ, while the number of tubercles is distinctly less than that occurring in the liver and spleen? It is apparent from these studies that there is no infallible parallelism between the size, nor even the number of tubercles developed in all the organs, as a result of the intravenous injection of dead tubercle bacilli and the original quantitative deposition of tubercle bacilli in these organs. The size of the tubercle in the organs of the guinea pig is therefore a direct index of the ability of the phagocytic cells to destroy tubercle bacilli, and the larger size of the splenic tubercle following the injection of dead bacilli is due to a more limited destructive power of the cells of origin of the tubercle in this organ for tubercle bacilli as compared with those of the lung and liver.

The amount of tuberculosis occurring in the guinea pig after the injection of bovine bacilli is greater than after the injection of a similar amount of dead human bacilli. The difference is more striking in the rabbit than in the guinea pig, which can be correlated with the susceptibility of these two species for the two types of bacilli, the rabbit being more susceptible to living bovine bacilli than to living human bacilli and the guinea pig being only slightly more susceptible to living bovine bacilli than to living human bacilli. No essential difference was noted between the organic tuberculosis occurring after the intravenous injection of living avirulent human tubercle bacilli and the intravenous injection of dead virulent human or bovine bacilli in guinea pigs, except that the pulmonary tubercles are larger with the living avirulent bacilli than with the dead bacilli. The splenic tubercle in both cases was larger than the tubercles in any of the other organs. An analysis of three guinea pigs, 32 days after the intravenous injection of 25

mgm. of avirulent human tubercle bacilli, revealed an average of 1.0 tubercle per high power field 136 micra in size in the lung, 1.1 tubercle of 80 micra in the liver, and 1.6 tubercles of 144 micra in the spleen, while the kidney and bone-marrow were essentially negative.

SUMMARY

One factor in organic susceptibility to tuberculosis is the inherent ability of the cells of origin of the tubercle in a given organ to destroy tubercle bacilli. In the four species of animals studied (guinea pig, rabbit, dog and monkey) the largest tubercle formed after the intravenous injection of dead tubercle bacilli in the organ which is the seat of the greatest tuberculous involvement following the intravenous injection of living bacilli. In the guinea pig the spleen becomes most involved after the intravenous injection of living bacilli and the tubercles resulting from the intravenous injection of dead bacilli are larger than in any other organ of the same animal. The rabbit's lung is most involved after the intravenous injection of living bacilli and contains the largest tubercles after the intravenous injection of dead bacilli. In the dog the liver is the most susceptible organ after intravenous infection with living bacilli; and the tubercles resulting from the intravenous injection of dead bacilli are larger in this organ than any other organ in the same animal.

Species susceptibility to the human and bovine strains of tubercle bacilli is correlated with the chemical constitution of the strain of tubercle bacillus in question, as related to the destructive power of the cells of origin of the tubercle in the various organs of the different animals for these bacilli. The human bacillus contains less lipoid than the bovine strain, and dead human bacilli are more readily destroyed by the phagocytic cells of the various organs of the rabbit than are dead bovine bacilli, which may in part explain the strikingly greater susceptibility of this animal to the bovine bacillus. The guinea pig, being susceptible to both strains of tubercle bacilli but slightly more so to the bovine, finds partial explanation in that the amount of tuberculosis developed in response to dead bacilli in the various organs is greater with bovine than with human bacilli, but this difference is not as marked as in the rabbit. Finally, the dog is equally susceptible to the bovine and the human strains of living bacilli, and no marked difference in the size of tubercles in the same organs was noted with the dead bacilli. The cell of origin and the nature of the tuberculosis occurring in the different organs of the different ani-

mals studied do not differ in kind in the animals given intravenous injections of living virulent human or bovine tubercle bacilli from those occurring in animals given intravenous injections of dead human or bovine tubercle bacilli. The only difference is one of degree.

The authors are duly grateful to Dr. Frank K. Williams for his kind assistance rendered during the course of the studies reported on in this paper.

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FIGURES

Description of Figures

FIG. 1. Photomicrograph of the lung of a rabbit that received intravenously a total of 300 mgm. of dead virulent bovine tubercle bacilli and 1 cc. of india ink per pound body weight. Note the number and size of the tubercles and the epithelioid cells containing carbon particles. At *A* subendothelial pericytes are causing a gradual obliteration of the lumen of a blood vessel.

FIG. 2. The same animal as in figure 1. Photomicrograph showing tubercles in the liver more numerous and smaller than those in the lung, and the epithelioid cells laden with carbon.

FIG. 3. Same rabbit as in figure 1. Photomicrograph of the spleen, showing the size and number of tubercles, with the epithelioid cells laden with carbon.

FIG. 4. Same rabbit as in figure 1. (High power.) Note the carbon-bearing epithelioid cells in the tubercle of the bone-marrow. There are red blood corpuscles in the spaces between the epithelioid cells.

FIG. 5. Photomicrograph (high power) of the lung of a rabbit given an intravenous injection of 300 mgm. of dead virulent bovine tubercle bacilli. Note the typical productive tubercle with a core of epithelioid cells and ring of hyperplastic histiocytic (?) elements.

FIG. 6. Photomicrograph of a tubercle in the spleen of the same rabbit as in figure 5, showing the smaller size and the nature of the epithelioid cells, which contain hemoglobin pigment and compose the tubercle.

FIG. 7. Photomicrograph of the liver of a rabbit which was given intravenously 600 mgm. of dead virulent bovine tubercle bacilli. Note the tendency for the formation of single giant-cell tubercles.

FIG. 8. High-power photomicrograph of the lung of the rabbit given an intravenous injection of 600 mgm. of dead virulent bovine tubercle bacilli. Note the productive tubercle with giant cells.

FIG. 9. Photomicrograph (high power) of the lung of the same rabbit as in figure 8. Note the intravascular tubercle with perivascular histiocytic (?) reaction, indicating the multiplicity of cells of origin of the tubercle in the lung.

FIG. 10. Photomicrograph of the lung of the same rabbit as in figure 8, showing the exudative pulmonary tuberculosis with giant-cell formation.

FIG. 11. Photomicrograph of the spleen of a rabbit receiving an intravenous injection of 600 mgm. of dead virulent human tubercle bacilli (*Gl.*). Note the tubercles in the spleen with Langhans giant cells and epithelioid cells containing altered erythrocytes and hemoglobin pigment. Note also the absence of tubercles in the Malpighian bodies.

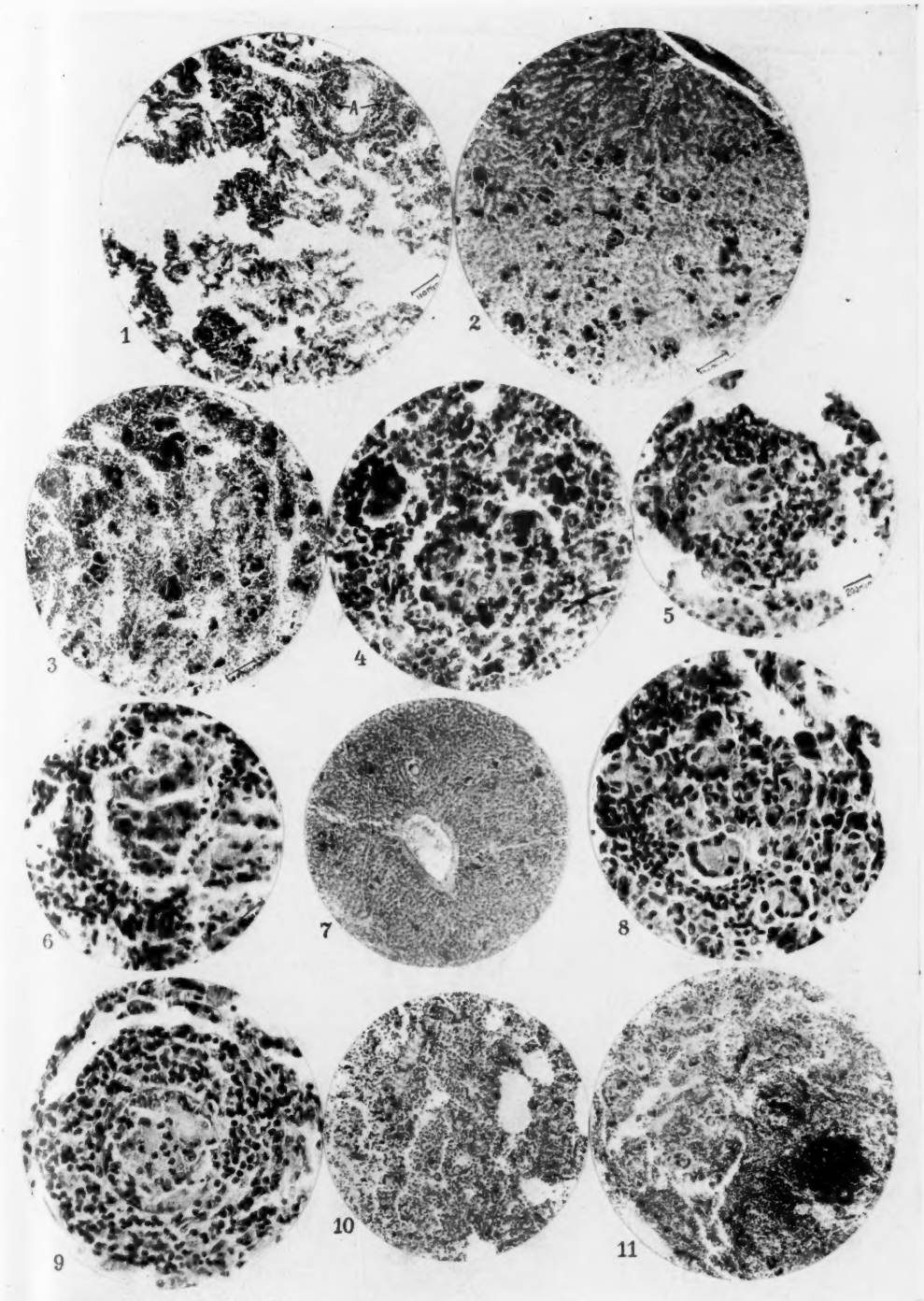
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FIG. 12. Photomicrograph of the lung of a rabbit given an intravenous injection of 600 mgm. of dead virulent human tubercle bacilli (*Gl.*). Note the obliterating endarteritis prominent in the lung of the rabbit after both living and dead bacilli.

FIG. 13. Photomicrograph (high power) of same lung as in figure 12, showing the character of the cellular reaction and the location of the proliferation.

FIG. 14. Effect of the strain of bacilli on the tubercle formation. Photomicrograph of the rabbit's lung after the intravenous injection of 300 mgm. of dead virulent bovine tubercle bacilli. Note the size and number of tubercles.

FIG. 15. The liver of the same animal as in figure 14. Note the size and number of tubercles.

FIG. 16. The spleen of the same animal as in figure 14. Note the size and number of tubercles.

FIG. 17. Effect of strain of bacilli on tubercle formation. Photomicrograph of the lung of rabbit given an intravenous injection of 300 mgm. of dead virulent human tubercle bacilli (*Gl.*). Note the size and number of tubercles. They are fewer and smaller than after the intravenous injection of an equal amount of dead virulent bovine tubercle bacilli.

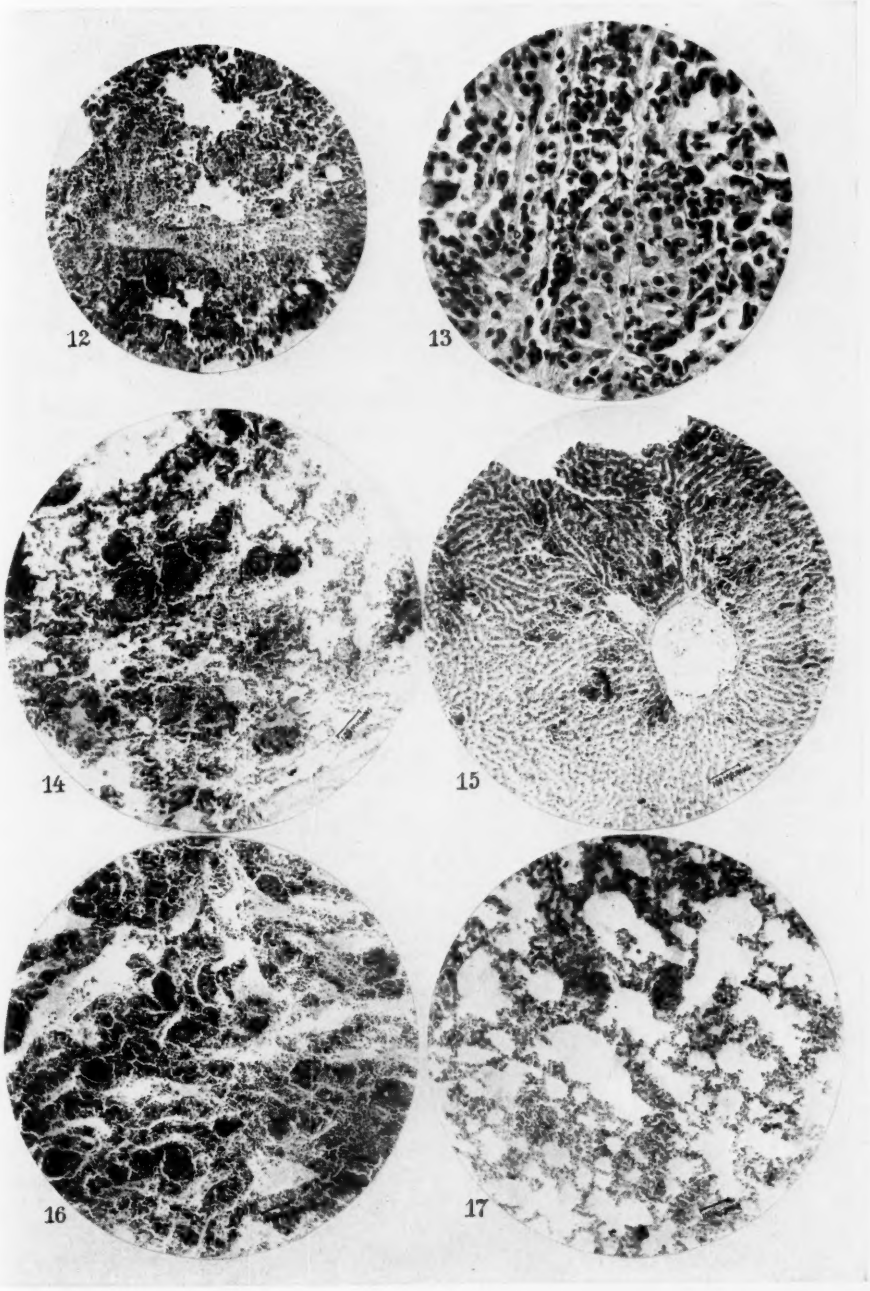
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FIG. 18. Photomicrograph of liver of same animal as in figure 17. Note that tubercles are slightly smaller and distinctly fewer than after the intravenous injection of an equal amount of virulent bovine tubercle bacilli.

FIG. 19. Photomicrograph of spleen of the same animal as in figure 17. Note that the tubercles after bovine bacilli are slightly larger, but the number after both human and bovine bacilli is about the same.

FIG. 20. Effect of dosage upon tubercles. Photomicrograph of the lung of a dog after the intravenous injection of 800 mgm. of dead virulent bovine tubercle bacilli and 1 cc. of india ink per pound body weight. Note the size and number of tubercles.

FIG. 21. Photomicrograph of the liver of the same animal as in figure 20. Note the size and number of tubercles and carbon-laden epithelioid cells.

FIG. 22. The spleen of the same animal as in figure 20. Note the size and number of tubercles with carbon-laden epithelioid cells in the pulp.

FIG. 23. Photomicrograph of the liver of a dog receiving 1000 mgm. intravenously of dead virulent human tubercle bacilli (*Gl.*). Note the fatty infiltration or degeneration of the central portion of the liver lobule, and preservation of the cells at the periphery, especially seen with large doses of dead bacilli.

FIG. 24. Photomicrograph of lung of the same dog as in figure 23. Note the acute exudative (polymorphonuclear) pneumonia.

FIG. 25. Photomicrograph of lung of dog given intravenous injection of 1000 mgm. of virulent bovine tubercle bacilli. This is another type of acute pneumonia, with marked desquamation of the epithelial cells of the alveolar walls.

FIG. 26. High power. Characteristic reaction of the spleen of the dog to large doses of bacilli. Same dog as in figure 25. Note the excessive destruction of erythrocytes and phagocytosis by splenic cells.

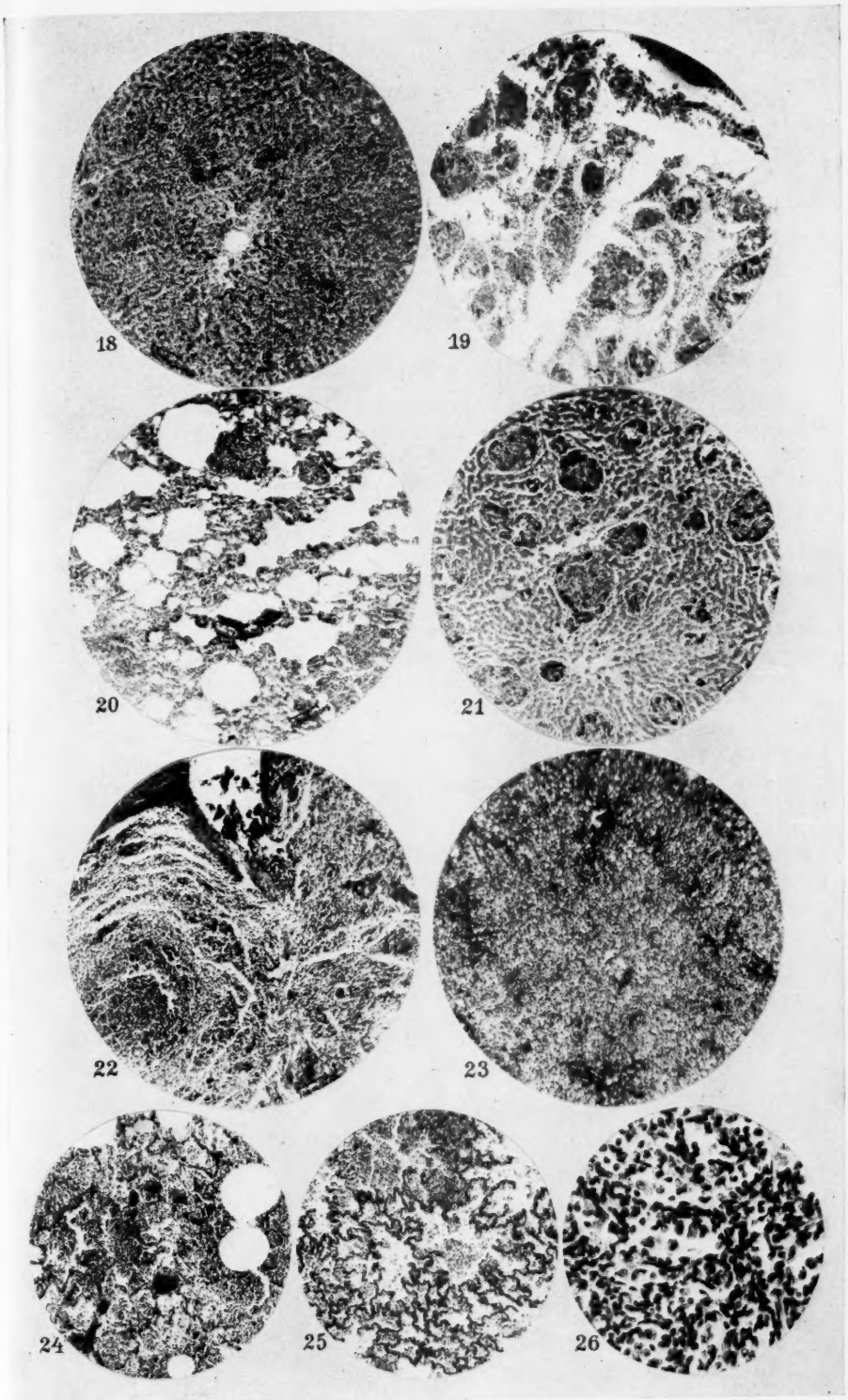
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FIG. 27. Tubercle-formation in the dog with smaller doses of bacilli. Photomicrograph of lung of dog given an intravenous injection of 200 mgm. of dead virulent bovine tubercle bacilli. Note the spindle-shaped character of the epithelioid cells in lung resembling those after living bacilli. There is spontaneous anthracosis and the carbon particles are deposited in the epithelioid cells of the tubercle.

FIG. 28. Characteristic tubercle in the dog's liver after large doses of bacilli. The same animal as in figure 30, given an intravenous injection of 1000 mgm. of dead virulent tubercle bacilli. Note ameboid character of the epithelioid cells.

FIG. 29. Photomicrograph of liver of dog given intravenously 1000 mgm. of dead virulent human tubercle bacilli. Note tubercle-formation about periphery of the lobule and the striking resemblance to that seen after living bacilli.

FIG. 30. Effect of dosage upon tubercle-formation in the dog. Photomicrograph of lung of dog given intravenous injection of 1000 mgm. of dead virulent human tubercle bacilli (*Gl.*). Note the size and number of tubercles. (Spontaneous anthracosis is noted in the tubercles.)

FIG. 31. Photomicrograph of liver of the same animal as in figure 30. Note size and number of tubercles.

FIG. 32. Photomicrograph of spleen of the same animal as in figure 30. Note the size and number of tubercles and the spaces between the epithelioid cells as compared to the close packing in the lungs.

FIG. 33. Effect of dosage on tubercle-formation in the dog. Photomicrograph of lung of dog after intravenous injection of 200 mgm. of virulent human tubercle bacilli. Note that the tubercles are slightly smaller and fewer than after the intravenous injection of 1000 mgm. of virulent human tubercle bacilli.

FIG. 34. Photomicrograph of liver of same dog as in figure 33. Note size and number of tubercles. The number is about the same as after 1000 mgm., but the size is distinctly smaller.

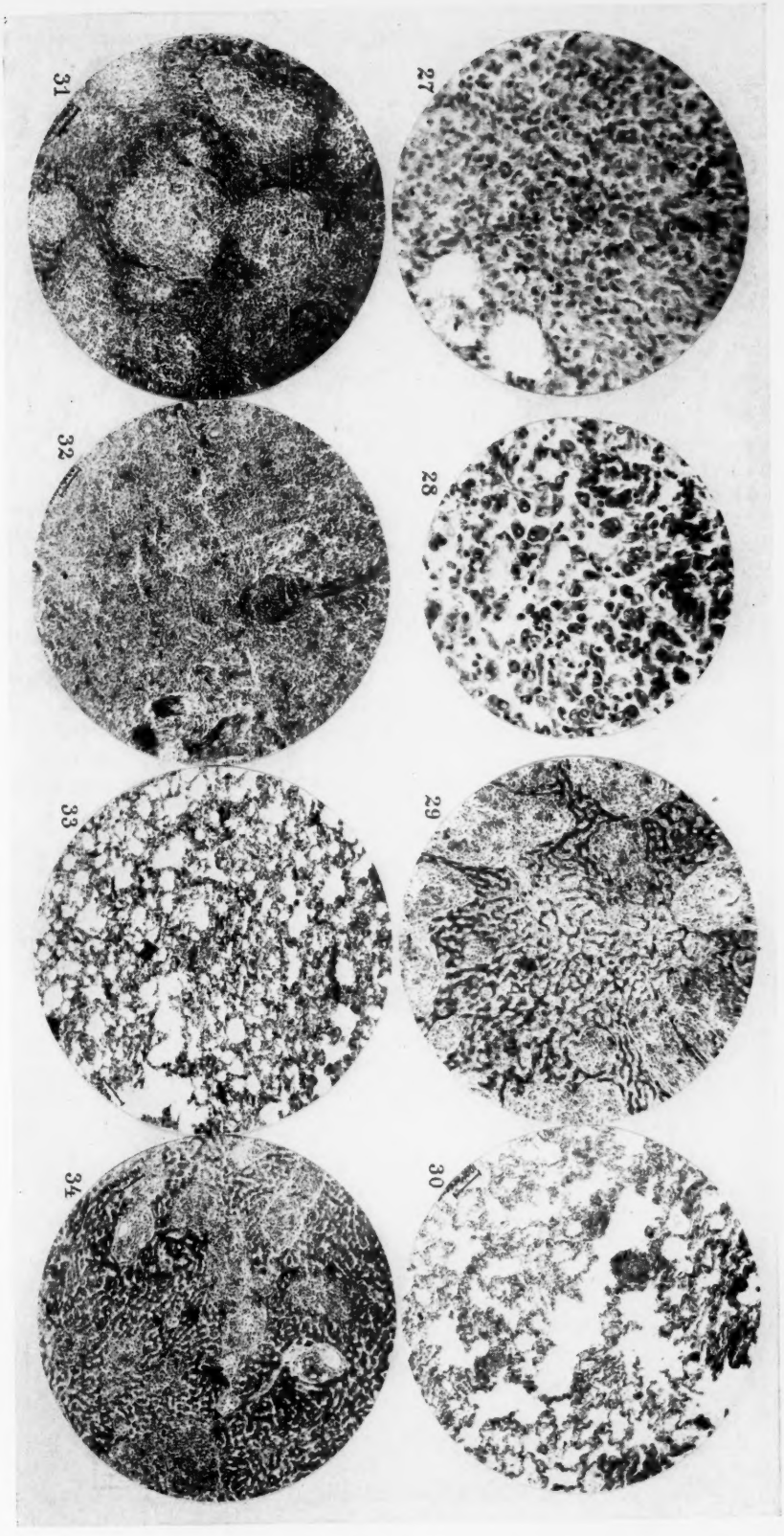
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FIG. 35. Photomicrograph of spleen of same dog as in figure 33. Note the single tubercle in the centre of the section. The tubercles are slightly smaller and one-half as numerous as after 1000 mgm.

FIG. 36. Photomicrograph of lung of guinea pig given intravenous injection of 50 mgm. of dead virulent human tubercle bacilli and 5 cc. of 1:5 dilution of india ink. Note the size and number of tubercles and the character of the epithelioid cells laden with carbon particles.

FIG. 37. Photomicrograph of liver of same animal as in figure 36. Note the number and size of tubercles and epithelioid cells laden with carbon particles.

FIG. 38. Photomicrograph (high power) of a tubercle, same as in figure 37. Note the carbon-laden epithelioid cells in the tubercle.

FIG. 39. Photomicrograph of the spleen of the same guinea pig as in figure 36. Note the number and size of tubercles and the carbon-laden epithelioid cells.

FIG. 40. Photomicrograph of lung of guinea pig given intravenous injection of 100 mgm. of dead virulent human tubercle bacilli. Note the characteristic picture. There are huge nodules of perivascular infiltration, not tubercles, consisting possibly of migrating lymphocytes or other like cells.

FIG. 41. High Power. Photomicrograph of lung of guinea pig receiving 100 mgm. of dead virulent bovine bacilli intravenously, showing the nature of the perivascular reaction. Note the perivascular cells consisting of three types: (1) Characteristic lymphocytes, with small deeply stained nuclei and faint rim of basophilic cytoplasm. (2) Larger cells, with larger vesicular nuclei and more basophilic cytoplasm. (3) Elongated cells with spindle-shaped nuclei, bent on themselves (*S*-shaped), and with fibrillar cytoplasm. The picture shows the migration of lymphocytes through the endothelial lining into the tissue spaces.

FIG. 42. Transformation of cells of perivascular nodules into typical epithelioid cells. Photomicrograph (high power) of lung of guinea pig given intravenous injection of 50 mgm. of dead virulent bovine tubercle bacilli. Note the upper area of lymphocytic (?) cells blending into and being transformed into lower epithelioid-cell area.

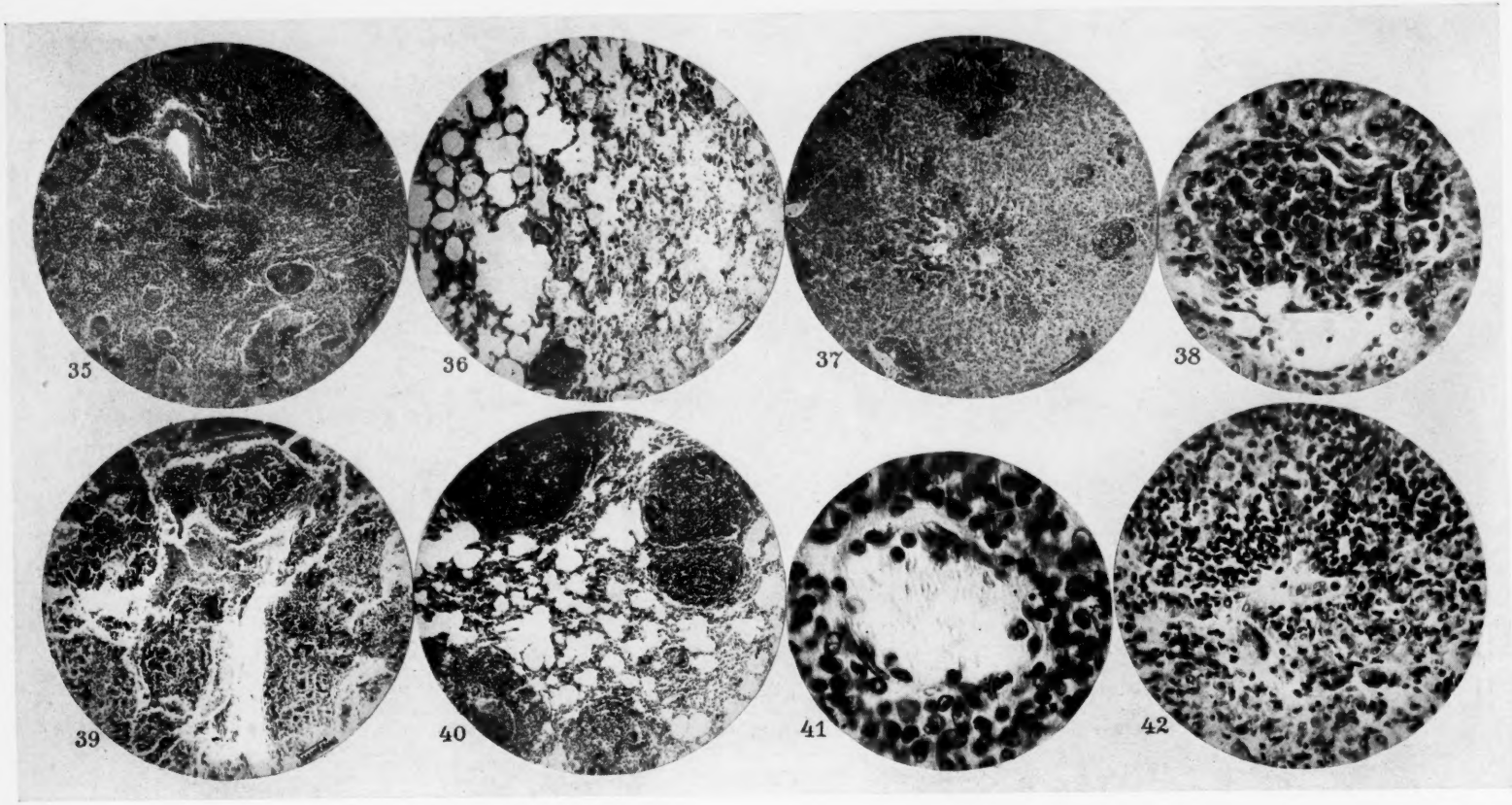
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FIG. 43. High power. Photomicrograph of lung of guinea pig receiving intravenous injection of 100 mgm. of dead virulent bovine tubercle bacilli. Note the tubercle originating in the alveolar wall by transformation of histiocytic (?) elements (periphery) into typical epithelioid cells (centre).

FIG. 44. Tubercle-formation in the organs of the guinea pig. Photomicrograph of lung of guinea pig given intravenous injection of 50 mgm. of dead virulent human tubercle bacilli. Note the size and number of tubercles.

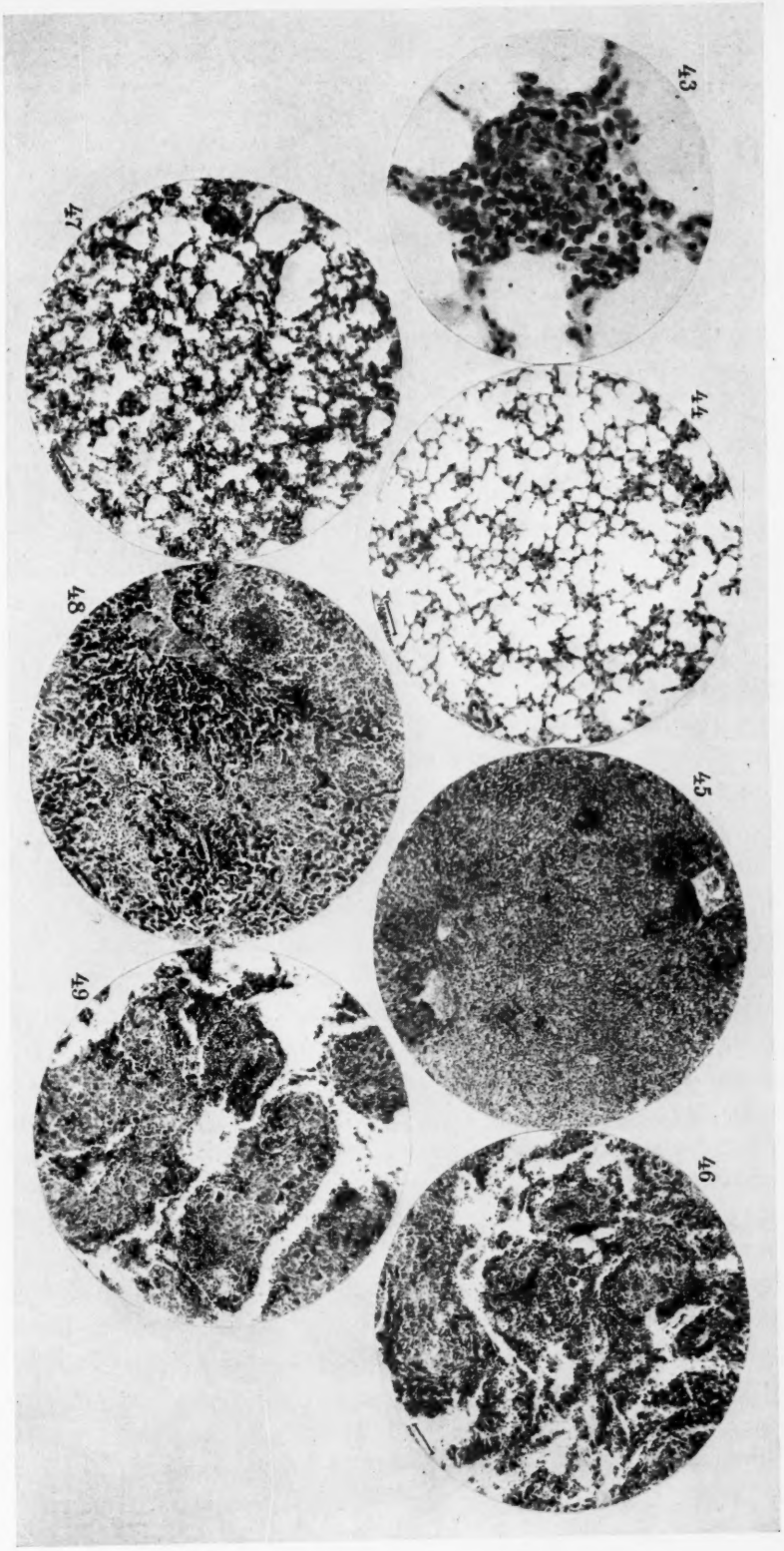
FIG. 45. Photomicrograph of liver of same guinea pig as in figure 44. Note the tubercles along the sublobular veins, consisting of a spheroidal mass of epithelioid cells and an occasional giant cell.

FIG. 46. Photomicrograph of spleen of same guinea pig as in figure 44. Note the size and number of tubercles. The size is much greater and the tubercles are more numerous in the spleen than in the liver.

FIG. 47. Tubercle-formation in the organs of the guinea pig. Photomicrograph of lung of guinea pig given intravenous injection of 150 mgm. of virulent human tubercle bacilli (*Gl.*). Note the number and size of tubercles as compared with those resulting from a smaller dose, shown in figure 44. The number of tubercles is greater but the size is approximately the same.

FIG. 48. Photomicrograph of liver of guinea pig receiving intravenous injection of 150 mgm. of dead virulent human tubercle bacilli. Note that the size and number of tubercles is greater than after smaller doses. There is necrosis in the tubercle. With large doses the tubercles of the liver are angular in shape as contrasted to the spherical shape with smaller doses. After large doses the tubercles resemble closely in histological characteristics the tuberculosis with living bacilli.

FIG. 49. Photomicrograph of spleen of guinea pig given intravenous injection of 150 mgm. of dead virulent human tubercle bacilli (*Gl.*). Note the almost complete transformation of the splenic tissue into tuberculous tissue.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PLASMA CALCIUM IN TUBERCULOUS ADULTS

E. M. GREISHEIMER[1] AND C. C. VANWINKLE[2]

For many years the idea of demineralization in tuberculosis has been prevalent although many investigators have shown that there is no disturbance in calcium metabolism in the disease. Halverson and his coworkers (1) found the normal range of calcium to be between 9 and 11 mgm. per 100 cc. of serum. In tuberculous individuals the range was from 8.4 to 11 mgm. In advanced cases the values tended to be lowest. The results were in agreement with those of some earlier investigators. Halverson also found that the calcium values tended to be higher in blood drawn after the noon meal than in that drawn in the fasting condition.

Howe and Medlar (2) found no evidence of an abnormal calcium metabolism in tuberculous patients. Barkus (3) found the calcium values in surgical tuberculosis to range between 10.16 and 10.83 mgm. except in the atrophic type, in which the average was 8.94 mgm. Sweany and his coworkers (4) found no constant relationship between the blood calcium and the stage of tuberculosis. In some of the hemorrhage cases the calcium was a little lower than in the other cases. The values ranged between 6 and 11.57 mgm. per 100 cc. of serum. Matz (5) found that the calcium content of normal serum was from 9 to 12 mgm. and that the calcium values of tuberculous patients were within these limits. Teplitz (6) found results which indicated a loss of calcium from the blood in the terminal stage of pulmonary tuberculosis.

With the idea of demineralization in tuberculosis firmly fixed in the minds of many, the natural sequence of events led to calcium therapy. Among the many who claim that beneficial results follow the administration of calcium salts are Prest (7), Ringer (8) and Beasley (9). However, Maver and Wells (10) found that the oral administration of calcium salts did not increase the amount of calcium in the blood and tissues in experimental tuberculosis, since this is normally maintained at a level not

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far below the saturation point of the body-fluids. Matz (5) found that the oral administration of calcium salts in tuberculous patients is followed by a rise in the calcium content of the blood. The administration of codliver oil likewise increased the blood calcium. Mason (11) found that 5 gm. of calcium chloride raised the plasma calcium 2.5 mgm. per 100 cc. in three hours, but he obtained no such effect by giving calcium lactate. Denis and Minot (12) could not increase the calcium of the blood of normal persons by giving 6 gm. of calcium lactate daily for periods of six to ten days. Teplitz (6) found that calcium alone, and calcium combined with thyroid extract, did not increase the serum calcium of tuberculous patients.

Since Hess (13) reported his results of sun-treatment in rachitic infants, many investigators have studied the effects of exposure of tuberculous patients to the sun's rays, or to the rays of the Alpine lamp. Many note marked improvement clinically, but Howe and Medlar (2) have made a chemical study of the blood during such treatments. They found that exposure to the Alpine lamp produced no effect whatever on the calcium content of the blood of tuberculous individuals. Their results have been confirmed by others. Greisheimer and Arnold (15) found that exposure to the Alpine lamp in cases of masked juvenile tuberculosis showed a slight increase in the plasma calcium, but just as great an increase occurred in the children who served as controls receiving no Alpine lamp exposure.

METHOD

A group of 55 patients between the ages of 25 and 51 years was selected. They were in various stages of tuberculosis, expressed as moderately advanced (b), moderately advanced (c), far advanced (b), and far advanced (c), according to the terminology used by sanatoria. Most of them were receiving only routine sanatorium treatment, but a few were being given calcium lactate, codliver oil, or lamp and sun exposure, in addition. They were all pulmonary cases, and many showed a complicating enteritis.

A record of the food eaten at the last four meals preceding the test was kept. The patients were instructed to drink no milk at breakfast or at midmorning nourishment on the day of the test, but a few of the group failed to follow instructions, as will be seen on the charts. The blood was drawn by syringe about four hours after breakfast and immediately mixed with 1 to 3 mgm. of heparin. The heparinized blood was sent to the

University laboratory, where the calcium of the plasma was determined three or four hours after the blood had been drawn. The method used was the Tisdall (14) method with slight modifications. Duplicate determinations were made. The difference between the duplicates was usually less than 1 per cent, but occasionally it rose as high as 2 per cent.

TABLE 1

Moderately advanced (b). Ca mgm. per 100 cc. plasma

AGE	WOMEN	MEN
25–30	*1. Under routine treatment:* None *2. Under special treatment:* None	*1. Under routine treatment:* E. C. H. 11.27 active E. W. J. 12.73 active R. L. 12.35 active *2. Under special treatment:* None
31–40	*1. Under routine treatment:* M. K. 11.75 active A. M. P. 12.34 very active *2. Under special treatment:* None	*1. Under routine treatment:* R. A. 14.15 quiescent *2. Under special treatment:* C. N. 14.42 quiescent, lamp and sun. W. T. 11.44 active, lamp and sun.
41–51	*1. Under routine treatment:* None *2. Under special treatment:* L. Y. 12.10 very active, lamp and sun; drank milk before test; died 10 weeks after test	*1. Under routine treatment:* None *2. Under special treatment:* G. M. 10.90 active; taking calcium lactate; drank buttermilk before test. T. V. 10.95 very active; cod-liver oil; drank milk before test; died 2 weeks after test.

RESULTS

The results of the patients classed as moderately advanced (b) are given in table 1.

It will be noticed in table 1 that there were 6 patients who were receiving only routine treatment. The average calcium content of these six cases was 12.43 mgm. There were two who were receiving lamp and sun treatments, and it will be noticed that the quiescent case has a higher calcium content than the active one. In the 3 patients who drank milk or buttermilk on the day of the test we find rather low values. One receiving

lamp and sun treatments showed 12.10 mgm. of calcium and was very active. This patient died ten weeks later on the operating table. One of the others was taking calcium lactate daily, and showed a calcium content of 10.90 mgm. The other was taking codliver oil, and the calcium content was 10.95 mgm. The last patient died two weeks after the test.

The results of the patients classed as moderately advanced (c) are given in table 2.

TABLE 2

Moderately advanced (c)

AGE	WOMEN	MEN
25–30	*1. Under routine treatment:* K. C. 10.9 active *2. Under special treatment:* None	*1. Under routine treatment:* None *2. Under special treatment:* H. D. 10.53 active, lamp and sun
31–40	*1. Under routine treatment:* C. H. 10.17 active *2. Under special treatment:* None	*1. Under routine treatment:* None *2. Under special treatment:* E. A. 10.50 active, lamp and sun
41–51	None	None

The average of the cases under routine treatment in table 2 was 10.53 mgm. of calcium. The average of those receiving sun and lamp treatments was practically the same.

The results of the patients classed as far advanced (b) are given in table 3.

There were 11 patients in the group shown in table 3 who were receiving only routine treatment. The average calcium content of these cases was 12.59 mgm. It will be noticed that the calcium content becomes a little lower as the age increases. There is not a constant difference between the degree of activity and the calcium content. There is no constant difference between the sexes. In the patients who were receiving some additional treatment, the highest value, 15.69 mgm., was found in an active case. This patient had milk before the test and was receiving lamp and sun treatments. The next highest calcium content, 15.6 mgm., was found in a patient who was in a very active stage of tuberculosis and who had had milk before the test. The lowest calcium value, 10.65 mgm., was found in a quiescent case receiving lamp and sun treat-

ments. It will be noticed that the administration of calcium lactate, codliver oil and parathyroid extract in one case did not appear to produce high calcium values.

TABLE 3

Far advanced (b)

AGE	WOMEN	MEN
25–30	*1. Under routine treatment:* C. B. 13.99 very active E. S. 12.42 active *2. Under special treatment:* E. N. 12.97 very active, drank milk before test. E. H. 15.69 active; drank milk before the test; lamp and sun. R. B. 12.34 active; lamp and sun; parathyroid extract. F. B. 13.05 active; taking calcium lactate. M. S. 12.05 quiescent; taking codliver oil.	*1. Under routine treatment:* P. W. H. 14.05 quiescent L. P. 12.22 very active, died 4 weeks after test. N. A. O. 12.81 active *2. Under special treatment:* L. N. A. 14.01 quiescent, lamp and sun.
31–40	*1. Under routine treatment:* A. L. 12.45 quiescent E. N. 12.86 active A. S. 12.15 very active *2. Under special treatment:* None	*1. Under routine treatment:* E. L. 11.52 quiescent *2. Under special treatment:* A. B. 11.21 active; drank milk before test. C. A. C. 15.6 very active; drank milk before test. C. N. 12.82 quiescent; taking calcium lactate. E. V. 12.37 active; calcium lactate, codliver oil; lamp and sun.
41–51	*1. Under routine treatment:* O. S. 12.33 quiescent *2. Under special treatment:* J. O. 11.37 active; calcium lactate and chloride.	*1. Under routine treatment:* E. P. 11.49 active *2. Under special treatment:* G. S. 11.85 quiescent; lamp and sun. T. T. 10.65 quiescent; lamp and sun. S. S. R. 11.78 active; lamp and sun.

The results of the patients classified as far advanced (c) are shown in table 4.

There were 8 patients listed in table 4 who were receiving only routine treatment. The average calcium content was 11.42 mgm. It will be noticed that in both the moderately and far-advanced groups the calcium content is lower in the (c) than in the (b) class of the routinely treated patients. The lowest calcium content was found in a patient who died the day following the test. The highest calcium content was found

TABLE 4

Far advanced (c)

AGE	WOMEN	MEN
25–30	*1. Under routine treatment:* F. C. 12.46 active N. R. 11.50 quiescent *2. Under special treatment:* R. B. 11.2 very active; codliver oil. T. F. 12.67 active; drank milk before test.	*1. Under routine treatment:* None *2. Under special treatment:* R. P. 11.11 very active; calcium lactate; died 8 weeks after test.
31–40	*1. Under routine treatment:* C. L. 13.2 active *2. Under special treatment:* None	*1. Under routine treatment:* A. S. 12.13 active *2. Under special treatment:* None
41–51	*1. Under routine treatment:* E. B. 10.27 active *2. Under special treatment:* A. B. 10.8 very active; taking calcium lactate.	*1. Under routine treatment:* L. W. 11.17 quiescent L. G. 9.93 very active; died day after test. G. S. 10.72 very active; died 7 weeks after test. *2. Under special treatment:* P. K. 16.4 very active; drank milk before test; taking calcium lactate; died 8 weeks after test.

in a very active case who was taking calcium lactate, and who had had milk on the day of the test. The patient died eight weeks after the test.

There were two women patients who were classed as far advanced (a). One of these, *E. N.*, aged 25 years, had a very active tuberculous lesion. She had had buttermilk just before the test. Her calcium content was 12.97 mgm. The other, *A. S.*, was 36 years old and classed as active. She was taking calcium lactate and showed a calcium value of 12.03 mgm.

DISCUSSION

The calcium contents of the plasma found in this study are somewhat higher than the serum values reported by other investigators. Greisheimer and Arnold (15) found that the calcium content of heparinized plasma was a little higher than the serum content of the same individual, the values being 10.64 and 10.07 respectively. Since the heparin by analysis shows no calcium to be present, this higher plasma value suggests that some calcium remains in the clot, thereby producing a lower serum value.

The taking of milk just before the test may have no effect on the calcium value, but the cases that did this are reported with those receiving special treatment, since their dietary conditions were slightly different. The very highest values found happened to be in patients who had had milk before the test; however, some others who had had milk did not show exceptionally high values. By looking over the records it was noticed that those who regularly drank milk five times daily showed a tendency to higher calcium values than those who usually refused it.

The administration of calcium lactate by mouth did not seem to produce high calcium values. Of course, there is a possibility that these cases may have shown a lower calcium value before the treatment was started.

Exposure to the Alpine lamp or sun did not seem to materially increase the calcium of the plasma. No doubt, lamp and sun treatment affects the calcium content in rachitic infants, but it seems without effect on tuberculous adults so far as the calcium content is concerned. However, there may be marked clinical improvement which does not lend itself to chemical measurements.

As a rule, patients in (c) of both the moderately and the far-advanced groups showed lower calcium values than those in (b). This would suggest that lower calcium content accompanies increased activity, yet cases which are clinically quiescent often show lower calcium than those which are clinically active or very active. The average of the seven terminal cases that died within ten weeks after the test was 11.92 mgm.

Of the 55 cases studied, 29 were men and 26 were women. In studying the results, no constant difference is found between the sexes. In studying the results according to age, no constant difference is found, although, as a rule, the younger the patient, the higher the calcium value.

SUMMARY AND CONCLUSIONS

1. The results indicate that tuberculosis is not characterized by a demineralization.

2. The higher values found in this study are due to the use of heparinized plasma rather than serum.

3. Patients who regularly drink a liberal amount of milk tend to show higher calcium values than those who refuse it.

4. The taking of codliver oil does not markedly increase the plasma calcium of tuberculous adults.

5. Exposure to Alpine lamp or sun does not increase the plasma calcium of tuberculous adults even when there is clinical improvement.

6. Patients classified as (c) show lower calcium values than those classified as (b) in both the moderately and the far-advanced groups.

7. There is no constant difference in calcium content as between the sexes.

8. There is no constant age difference although the tendency is toward lower calcium values with increasing age.

The authors wish to express thanks to those of the laboratory, dietetic and clinical staff, who have helped to make possible this study.

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RECENT ADVANCES IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

EDOUARD RIST[2]

My first words shall be a heartfelt expression of thanks to your Association for having invited me to speak before this meeting. There is no tuberculosis association in the world to which the world is more indebted than to yours, for methods, examples and achievements. You have shown us how, through the coöperation of the scientific mind with the spirit of citizenship, a whole country can be aroused, persuaded to follow willingly and enthusiastically the call of eminent leaders, and organized under self-imposed discipline, in order to solve one of the most intricate and difficult social and medical problems which lay before civilized mankind. The strikingly rapid decline of the tuberculosis death-rate in the majority of your States and larger cities is in itself the best illustration of the magnitude of your efforts and the soundness of your policy. To the European student of tuberculosis, the perusal of your statistical figures is a constant source of encouragement. And he finds some of his best inspiration in the splendid contributions which American research workers and clinicians bring to our common enterprise in the monthly journal which you publish and in the reports of your yearly meetings. How could he appear in your midst and be admitted to take part in your discussions without a feeling of deep and friendly gratitude?

Unfortunately I am bound to confess that there is, mixed with this feeling, something in me, which, I think, the word "awe" only can express adequately. Many months ago, your Managing Director, my dear friend, Dr. Linsly R. Williams, wrote to ask me if I would be willing to address you on *Recent Advances in the Treatment of Tuberculosis*. I agreed to the topic with truly French lightheartedness. But when it came to thinking about it and to trying to put my ideas in order concerning those "recent advances," I felt exceedingly distressed. It seemed, at first view, as if such advances as there are were not altogether

[1] An address, delivered at the General Session of the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 4, 1926.

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recent, and also as if the really recent ones were not real advances. I am sure some of you feel the same way, and I call upon them to help me with their sympathy.

My task will be easier, I think, if you allow me to use the word "recent" in a more or less broad sense, neither extending it to half a century or so, as we are still wont to do in slow-going Europe, nor limiting it to a couple of years or months, as you Americans are inclined to reckon. Let us follow a medium path, and compare the chances of lasting improvement or of recovery which a consumptive patient had, say twenty-five years ago, with the prospects of healing which he has nowadays. Many of us have had a personal experience extending over that length of time and are able therefore to judge for themselves. The result of such a comparison is unequivocal. The prognosis of consumption, provided the patient comes under competent care, has been improved to a considerable degree. The proportion of cases which are not only arrested but restored to normal health, with an unimpaired capacity for work, is constantly increasing. The lifework of a tuberculosis specialist, even in the best equipped sanatoria of a quarter of a century ago, was nearly as sad and monotonous as a surgeon's in pre-Listerian days. It required a character of quite exceptional devotion and fortitude to limit one's medical activities to a disease almost invariably fatal. To-day the tuberculosis specialist has no longer reason to envy his colleagues in other fields of medicine. He has his good share of gratification and reward. His ministrations are no more a helpless and smilingly tragic effort toward a prolonged euthanasia. His conscious and often successfully attained aim is to *cure*.

That such a change is due solely to new and improved procedures of treatment, no one can honestly deny. Let us see how it came about.

Among the four methods which one can logically consider, two only were at our disposal at the beginning of our century: (1) the classical *air and rest cure* (which, thanks to the persevering efforts of Brehmer and Dettweiler in Germany, of Bennett in Great Britain, of Grancher and Küss in France, and in this country, of that saint-like figure, Trudeau, had almost reached its stage of perfection) and (2) the *immunological method*, embodied in tuberculin treatment, which Robert Koch had initiated. Of (3) *chemotherapy* applied to tuberculosis some people dreamed perhaps; but Ehrlich had not yet set before the scientific world the basic principles of the chemotherapy of infectious diseases in general, and such attempts as had been made toward the healing of tuberculosis

by drugs were entirely empirical and unsuccessful. Of (4) *collapse therapy*, advocated as far back in the past as 1819 by the great English physiologist, James Carson, and persistently studied by Potain in France in the eighties, it seemed uncanny to speak. Although Forlanini (of Pavia), who had published his first cases of successful artificial pneumothorax in 1894, pursued his solitary researches with admirable perseverance, in spite of scorn and indifference, although your great surgeon, John B. Murphy, had come forward before the Congress of the American Medical Association in Chicago in 1898 to tell the story of several consumptive patients whom he claimed to have cured by the same method, collapse therapy really was as if it were not.

It is interesting to compare the fate of those four methods during the last twenty-five years.

The *air and rest cure* has stood the test of time. As I have said before, it had obtained such a degree of perfection at the beginning of the period which we have in mind, that one can hardly speak of improvements in its application. Even such adjustments as graduated exercise and work were implied in its early principles; and I do not think that the claims made to assimilate them to an hypothetical auto-tuberculin cure are very sound or very wise. Let us notice, however, that the services of the air-and-rest cure have been made available to a considerably greater proportion of tuberculous patients through better organization. The number of public and private sanatorium beds has been and still is increasing in almost every civilized country. Provisions have been made for more prolonged cures. The remarkable advances, which the development of X-ray examinations, the more accurate techniques for detection of tubercle bacilli and also the evolution of our ideas concerning the pathology of tuberculosis at large, have brought about in our diagnostic methods have noticeably reacted on the efficiency of sanatorium treatment. Early cases are more readily recognized; nontuberculous cases are more easy to eliminate. There can be no doubt therefore concerning the air-and-rest cure. It is better applied nowadays than it was formerly and it remains the *sine-qua-non* foundation of whatever treatment one might undertake against tuberculosis. Should research ever enrich us with a therapeutic procedure, which would cure tuberculosis as antitoxin cures diphtheria or as salvarsan cures syphilis, I am convinced that the air-and-rest cure would be as necessary as ever,

and that nowhere would the craved-for remedy be applied under better conditions and with more success than in a santorium.

But it must be admitted that the proportion of cases which can be restored to health by sanatorium treatment alone is, after all, small. The best available statistics show us that the really lasting satisfactory cures are scarce, and that the death-rate of patients having had bacilli in their sputum remains high. We all know very well that, if we had nothing else to offer our consumptive patients than the classical air-and-rest cure, we could not boast to-day of any noteworthy advance in treatment, because only the incipient cases would be within the scope of our therapeutic efforts.

Has the *immunological method* a better record? It is rather significant in this respect, that, on the program of this, your twenty-second annual meeting, not a single paper is announced dealing with the treatment of tuberculosis by tuberculin or its derivates. When one remembers the enormous amount of literature devoted to that topic in prewar days, one cannot but be struck by the lack of interest which generally prevails at the present time concerning the therapeutic use of tuberculin. Contrary to sanatorium treatment, it has certainly not stood the test of time. Not only has the massive dosage procedure advocated by Koch been abandoned long ago, because it was fraught with many dangers, but even the minimal, reactionless dosage, which, under the influence of Sahli among others, has been so universally applied to consumptive patients, has proved to be of no great value. Tuberculin has been given a fair trial. It has failed.

I know that, by saying so, I shall probably shock some of the faithful few, who still honestly adhere to the myth of tuberculin being the specific treatment of tuberculosis. But I think they are under a delusion. One should always keep in mind that no experimenter has ever succeeded in healing any form of tuberculosis in the animal by the use of tuberculin. This is a negative fact, of course. But it is basic; and one ought to recall it emphatically at the opening of any discussion whatever on the therapeutic use of tuberculin.

I do not mean to say that tuberculin is not specific, nor that it is without effect on some tuberculous lesions. I am convinced on the contrary that what is called the focal reaction, namely the hyperaemic and inflammatory changes which a hypodermic injection of tuberculin determines at the site of the specific lesion, is often followed by a tendency to

form scar-like fibrous tissue, as one can observe when treating tuberculous lesions which are easily controllable by the eye, like lupus of the skin or subcutaneous tuberculous adenitis. Unfortunately, tuberculous lesions of the lung are much more difficult to control, and they are apt to extend and to ulcerate under the influence of a focal reaction, with the result that the patient gets worse instead of getting better. On the other hand, if we undertake to put a skin or lymph-node tuberculosis under the beneficial influence of a series of focal reactions, we readily notice that in order to obtain such reactions, we have to increase the dosage at a rate progressing with amazing rapidity. After a short time, even the most massive doses fail to give a reaction and consequently to be efficient. Immunity to tuberculin, which is by no means synonymous with tuberculosis immunity, has developed. If the lesion is so small that it can be healed with only a few focal reactions, before this condition of tuberculin immunity has been obtained, we may speak of a successful cure. But in the vast majority of cases, we fail, long before the lesion is healed, to get focal reactions even with the largest doses (I have given as much as 3.5 cc. of pure tuberculin in a single dose, without any local or general reaction, in a case of lupus); and the treatment has to be abandoned. Such are, I believe, the essential reasons why tuberculin treatment, as it was advocated by Koch, though undoubtedly active in a way, has an exceedingly limited scope.

If we use tuberculin after Sahli's principles, namely, beginning with minimal doses which are very slowly increased, and avoiding carefully any kind of general or focal reaction, we certainly get rid of many of its dangers. But, at the same time, we deprive the patient of its benefits, which are entirely dependent upon the focal reaction. To-day, after more than twenty years, during which hundreds of thousands of patients have been submitted to this modified tuberculin treatment, its most serious followers have nothing more to say in its favor than that it is helpful in cases of mild, very limited pulmonary tuberculosis, having a spontaneous tendency to healing and a normal temperature. I think the simple air-and-rest cure is more—and justly more—ambitious than that. And I never could help wondering why the believers in Sahli's method did not undertake to prove its efficacy by using less disputable criteria. If one could demonstrate to us a few hundred cases of bone and joint tuberculosis healed by tuberculin only, how gladly we would apologize for our previous lack of faith! But you know that it is not so.

It would be futile, I think, to mention the countless modified prepara-

tions of tuberculin, which all claimed to be more active and less harmful than Koch's old tuberculin. It would be equally futile to consider the various attempts at vaccine treatment by bacillary emulsions and extracts or more or less defatted abstracts, or the partial antigens, of which some have been conscientiously tried by honest research workers, while others have been advertised to the medical and nonmedical world with a strong and decidedly unpleasant flavor of commercialism. Of course, passive immunization by serum therapy has had its short golden days. But the first condition for such a treatment, namely the active immunization of the serum-producing animal has never been realized so far. And the light-hearted explorers who thought this condition unessential have failed lamentably.

If, therefore, the prospects of healing our consumptive patients have improved, it is certainly not due to any significant advance in the immunological methods of treatment.

Let us turn now to *chemotherapy*. Several workers have been busy these last years trying to open a way into that new field of investigation. Various compounds of copper or gold and other metals, various derivatives of codliver oil or of chaulmoogra oil, were tested. Nothing definite or convincing had been brought to light—interesting though some of those attempts may be—until, two years ago, news which seemed very bright and hopeful, came from Denmark and was at once received with keen sympathy all over the world. Auro-thio-sulphate of sodium, or *Sanocrysin*, has had the rare good fortune of being accepted almost at once by the tuberculosis experts of every civilized country as a discovery well worth being tested seriously. The principles, which had led Moellgaard to recommend its use against tuberculosis, seemed sound and in conformity with Ehrlich's postulates. The results of animal experiments, as reported by him, looked just like those which one would theoretically have expected from a substance able to destroy large quantities of tubercle bacilli *in vivo;* namely, the outbreak of toxic phenomena similar to those which are determined by tuberculin. It was not unreasonable to suppose that an intoxication of this nature could be efficiently neutralized by an antituberculin serum; although the apparent ease with which such serum was obtained, by using a method not essentially different from those which had been unsuccessfully tried by so many workers in the past, was a matter for some astonishment. Last, but not least, one could not but be impressed by the fact that Sanocrysin

was being tried with all the necessary cautions, in the public hospitals and sanatoria of a country which we all rightly admire for the methodical and conservative spirit of its medical school and its physicians, as well as for its thorough and efficient organization of the fight against tuberculosis. When men like Thorwald Madsen and Knud Faber,—whom I feel, like some of you, I am sure, privileged to be allowed to regard as personal friends,—when men of such deservedly high ethical and scientific authority come forward, and recommend the therapeutic use of a new compound against tuberculosis, we can do but one thing,—listen to them and try.

Sanocrysin has been tried, honestly tried, under conditions, which I think, are the most favorable one could wish for. In many countries, tuberculosis experts of recognized competence have been entrusted, more or less officially, with the experimental and clinical study of the new remedy. Their reports, containing the histories of all the treated cases, have been published. One cannot but confess that the reading of those reports has been a cause of disappointment and disillusionment. Of the initial theoretical foundation of Moellgaard's treatment, hardly anything remains to-day. The toxic symptoms determined by Sanocrysin have certainly nothing in common with tuberculin shock. They are very similar to those of poisoning by a metallic substance, like mercury. The dermatitis, the stomatitis, the digestive troubles, the nephritis are easily explained by such an intoxication. Consequently, the use of the specific serum to counterbalance those symptoms has been abandoned.

But the first theoretical explanation of experimental facts may prove incorrect, and yet the facts be true. Unfortunately, research workers who undertook to repeat Moellgaard's animal experiments failed to get the favorable results which he had announced. Soon after his book had appeared, I began, with the coöperation of J. Rolland and E. Coulaud to treat with Sanocrysin, in my laboratory, quite a number of guinea pigs and rabbits made tuberculous less than a week previously by subcutaneous or intravenous inoculations of bacilli. We followed exactly the technique and dosage recommended by Moellgaard. A good proportion of the treated animals died early, as a consequence of the toxic properties of the gold compound. The rest died within the same period as the control animals, and showed tuberculous lesions not in the least less severe or less generalized than the controls, which, injected at the same time and with the same amounts of bacilli from the same culture, had

not been treated. Nevertheless, suspecting that our experiments might have been unwillingly faulty, and that perhaps they had not been pursued on a large enough scale, we refrained from making them public, until the similar experiments of Calmette in France and of several workers in other countries convinced us that we had not been mistaken.

Yet Sanocrysin may be more efficient in clinical than in experimental tuberculosis, although the results are much more difficult to appreciate soundly. This last assumption proved no less delusive. My personal experience with Sanocrysin therapy in hospital patients entirely confirms what has been said and written by the large majority of clinicians outside Denmark. The untoward effects of the metallic poisoning by gold are by no means negligible. They can be reduced to a minimum by careful dosage; but even so they may be fatal. In most cases the disease is not influenced by the drug. The cases which do well—and they are small in number—are of such a nature that one is inclined to think that they would have done quite as well without any drug treatment, under the simple influence of the old air-and-rest cure, the beneficial effects of which one is always too prone to forget. In patients who had been improving, either spontaneously or under the classical treatment, one may observe that during a course of Sanocrysin the evil symptoms appear again and the lesions extend. Finally,—and this, in my opinion, is very important,—it has been unanimously admitted, even by the Danish authors, that tuberculosis of the lymph-nodes, of the skin, of bones and joints, is in no way influenced favorably by Sanocrysin.

I should not like to appear unduly pessimistic, and I am ready to concede that in some of the cases which have improved Sanocrysin may have played some part in the improvement. But, whatever part it may be, it is slight. Let us prolong the experiment and leave the discussion open. Let us find out patiently and scrupulously whether such beneficial properties that may lay hidden in gold cannot be enhanced and made more active. But let us agree also on the fact that Sanocrysin, as a chemotherapeutic procedure against tuberculosis, can in no way be compared to Salvarsan in the treatment of syphilis. The latter has rapidly and unquestionably proved its curative power. Of the former, we positively know that it can do much harm; and there is still legitimate doubt as to whether it can do any good.

Nevertheless, and even if some day the idea of treating tuberculosis by Sanocrysin has to be abandoned, the transient fame of that substance will not have been altogether useless. It has compelled us to be less

forgetful of the natural course of tuberculosis, to study with a clearer and more critical mind the histories of our patients, and to discover again that old truth, which, it seems, has still to be rediscovered from time to time; namely, that there is such a thing as spontaneous improvement and recovery from even apparently severe forms of tuberculosis of the lung, and that rest in bed is the best means to favor such spontaneous processes. On the other hand, we have been taught once more how delusion and error are difficult to avoid and how carefully we must guard ourselves against them. Even the best scientific minds, associated with the highest moral character, can occasionally be misled. In that respect, the story of Sanocrysin sets before us not only a therapeutic but also a psychological problem of no common interest.

We are therefore driven to the conclusion that the considerable advances which it has been our generation's privilege to witness in the treatment of tuberculosis are due solely to one cause: namely, the rapid and universal development of that purely mechanical method, which we call *collapse therapy*. Artificial pneumothorax, the early history of which dates back to more than a century ago, is based on the soundest anatomical and physiopathological principles. The reason why it took such a long time before it was considered seriously is easy to explain. Two conditions, of which James Carson could not possibly have had even a dreamy anticipation, were indispensable to its being made a safe and controllable procedure: first, the advent of aseptic surgery, which put an end to the previously almost unavoidable risk of severe infection attending the simple puncture of the pleural cavity; and, second, the discovery of the X-rays, which enabled us to explore the inside of the chest and to observe the pathological changes in the lung with unprecedented clearness and accuracy. The progress and improvements of artificial pneumothorax have run exactly parallel with the progress and improvements of roentgenological technique.

That artificial pneumothorax is the greatest—I feel almost tempted to say, the only—recent advance made in the therapy of pulmonary tuberculosis, who can seriously doubt to-day? There is no hospital department, no sanatorium, no institution whatsoever, specializing in the treatment of consumption, where artificial pneumothorax is not practised and where it is not considered essential. There is not a competent physician, who, after having examined a new consumptive patient, does not ask himself first, "Is artificial pneumothorax possible in his

case or not?" The prognosis, the future, the life of the patient are dependent upon the answer.

I shall not dwell to-day on statistics, reserving them for another paper to be read before your Clinical Section. But I would emphasize one point only, namely, the fact that, whereas the air-and-rest cure's object is practically limited to the arresting of initial cases, whereas tuberculin at its best can only claim to play an auxiliary part in the treatment of mild, afebrile forms having a spontaneous tendency to healing, artificial pneumothorax wins its most striking successes in cases, which, before its advent, would have been regarded as hopeless, in cases in which the lesions are extensive and excavated, the sputum is abundant and the fever high. It is not only capable of putting an end to those symptoms, to stop the progress of the lesions and to cicatrize them; it is not only capable of reducing the sputum together with its bacillary contents to nought, and therefore to make the patient a harmless member of his family and of his community. It can restore him unconditionally to health, with a full capacity for work. Consumptive women treated by artificial pneumothorax regain the rights of motherhood: they can bear healthy children and bring them up. Who could have dreamed of such achievement twenty-five years ago, except that silent, solitary, neglected man in Pavia, Forlanini? But he knew he was on the right path. He knew his day would come. His day has come. And it is a matter for gratification to feel that, when the old master died, he had seen the glorious dawn of that day.

At first, the induction of an artificial pneumothorax seemed to be legitimate in a very small proportion of cases only. But the proportion has increased to a considerable degree and is still increasing. Thanks to the advances made in the technique and interpretation of X-ray plates, we have been led to assume that, practically, unilateral pulmonary tuberculosis is really much more common than was admitted. We have been taught also that cavitation, undiscoverable by the ear, is present in many a case which would have been considered formerly as a mere incipient infiltration not justifying collapse therapy. One may say, I think, without exaggeration that at some period of their history the majority of consumptives who die have been at least temporarily in a condition justifying artificial pneumothorax. The problem laid before the physician is not to let that period pass without seizing the opportunity.

But unilaterality is not the sole condition for success in artificial

pneumothorax. The pleural space must be free. Small and limited adhesions are not necessarily an obstacle to efficient collapse. If they are string-shaped and prevent the complete shrinking of a cavity, they may, under favorable circumstances rupture spontaneously. In some cases, it will be possible to destroy them by the thoracoscopic procedure so ingeniously built up and so dexterously executed by Professor Jacobaeus of Stockholm. But it is an unusually difficult intervention, not always completely successful, and probably destined to remain rather exceptional. Large pleural adhesions make the establishment of an artificial pneumothorax absolutely impossible, and it is a cause of great disappointment when, in a case otherwise perfectly suitable for such treatment, the attempts to introduce nitrogen or air into the pleural cavity fail for that reason. But, at this juncture, the surgeon may find his opportunity, as John B. Murphy had already foreseen twenty-eight years ago. The considerable improvements, which have been made recently in the technique of extrapleural thoracoplasty, have changed this once rather terrifying operation into a procedure, which is getting more and more safe and which has not only saved many lives but has restored to health and normal activity many a patient who had, for years, been a bedridden sufferer. I am convinced that thoracoplasty has not yet shown all that it can do, and that we are entitled to expect from it more than we already possess. The advances in that line depend on a closer coöperation between the physician and the surgeon. Brauer, Saugman, and Gravesen have shown us that they can coöperate in one and the same person. May I add that the coöperation of the patient is no less necessary? It is often difficult to persuade him that the condition of relatively tolerable equilibrium which he enjoys is much more unstable than he is naturally inclined to believe, that sooner or later his sound lung will be diseased in its turn, and that his general resistance will be diminished. Not the present moment, but the future must be considered. Not as a last and desperate resource, when everything is lost, but as a preventive and protective measure, taken in time, when all the conditions are favorable, against a more or less distant but unavoidable danger, must the operation be proposed and accepted.

But, of course, the collapse determined by thoracoplasty has one great disadvantage, not to speak of the operative risk and the deformity which it implies: it is a permanent, irrevocable collapse. The function of the shrunken lung is lost forever. Therefore artificial pneumothorax, which, in a large proportion of cases, allows the once diseased lung to be restored

functionally, must always be preferred, whenever it is possible. Thoracoplasty is a substitute for pneumothorax when the latter has proved impossible or inefficient. It is not an equivalent, and should never be regarded as such.

Surgery can help us in still another way. Unilateral phrenicotomy results in a complete paralysis of the corresponding half of the diaphragm, which is passively lifted up and immobilized, thus producing a very noticeable collapse of the lower third of the lung. When the tuberculous lesions are limited to the inferior part of the lung, and especially when they are situated in the immediate neighborhood of the diaphragm, this very harmless operation, which Stuertz was first to advocate, is able to render great service. There has been a tendency in certain quarters to generalize the use of phrenicotomy, to submit to it cases in which the lesions are predominantly apical, and even to recommend it preferably to artificial pneumothorax. This, I think, is very unwise. The indications for phrenicotomy alone are limited, in my opinion, to a small proportion of cases, and, even then, only when pneumothorax has been found unfeasible. But, in combination with pneumothorax (for instance when the collapse is only partial and the diseased lower lobe remains adherent), and also in combination with thoracoplasty, phrenicotomy is a non-negligible factor in the mechanical therapy of lung tuberculosis.

Meanwhile, artificial pneumothorax itself has had its technique improved in many ways. The very awkward danger of gas embolism, which gave us all so much anxiety at an early period, has almost entirely disappeared. We no more regard the fluid exudates, occurring sooner or later in 60 per cent of the cases, as a serious drawback. We do not hesitate to tap them; and, even when they become thick and turbid, even when they become fistulized, we do not think the game is lost. Recently a French physician, Dr. Bernou of Châteaubriant, has thought to substitute paraffine oil containing a mild antiseptic (essence of niaouli) for the puriform or purulent effusion, and even to fill up ultimately the entire pneumothorax cavity with such oil. *Oleothorax* has proved to be a valuable method. It is often able to maintain an efficient collapse of the lung and to prevent the formation of those otherwise uncontrollable adhesions, which so often follow long-standing exudates and prematurely put an end to pneumothorax treatment.

Perforation of the collapsed lung has been from the beginning, and deservedly, considered one of the most fatal complications of artificial

pneumothorax. It is still so. But it is encouraging to remark that some of these cases can escape death nowadays if they are treated in time by a thoracoplastic operation. And, if we finally turn to the most frequent obstacle to success in artificial pneumothorax, namely to the development of contralateral lesions, we also find that the prognosis of such lesions is no longer as desperate as it was formerly. Experience has taught us that the collapse of the primarily affected lung need not necessarily be prematurely abandoned. If it is maintained and the patient is put on prolonged bed-rest, the contralateral lesions may sometimes heal spontaneously. If the collapse of the primarily affected lung has lasted long enough, and we may presume that it has resulted in healing, we may let the pneumothorax on that side resorb, and induce an artificial pneumothorax on the other side. One may even be led, the danger being urgent, to induce the pneumothorax on the contralateral lung before the first pneumothorax has entirely disappeared. It is surprising to see how extraordinarily well such a double pneumothorax is tolerated by some patients. This remark led some physicians deliberately to induce a bilateral pneumothorax in some well-chosen cases of primarily bilateral tuberculosis. It seems, of course, a rather bold step, requiring a faultless technique, absolute bed-rest and very careful nursing. It should be reserved for cases in which the lesions are progressing rapidly and one feels that there is nothing to lose. That among such cases treated by bilateral pneumothorax there are many who gain nothing, it would be foolish to deny. But there are also quite a number who are indisputably saved from impending death and who ultimately seem to do almost as well as successful cases of unilateral pneumothorax. It is really very wonderful to observe some of these patients under the fluoroscope, to see them breathe with their two collapsed lungs, having a vital capacity which may be reduced to less than 20 per cent, and yet having a normal rate of respiration and showing, at least when at rest, no sign of dyspnoea.

I mentioned the last-named recent advances only to show that collapse therapy has not yet said its last word, that we have the right to expect from it still more benefit than it has already given us at the present time. And yet, one must never forget that the mechanical treatment, though it has so amazingly improved the prognosis of consumption, is not a specific treatment. It does away with the mechanical obstacles which prevent the spontaneous healing of the disease, and does nothing more. It creates nothing. Its practice has shown us how powerful those

mechanical obstacles are to oppose spontaneous healing, and how strong the tendency to spontaneous healing is in a large proportion of patients, even when they are affected with very severe lesions. But we all know very well that, in order to really conquer tuberculosis, much more is needed than collapse therapy.

Who can foretell whence the specific therapy will come? Chemotherapy is still in its infancy. Surely it will grow. From immunological methods we have still many gifts to expect. Active immunization of cattle against tuberculosis, it seems, will soon be within reach. At least Calmette's patient and careful investigations on the immunizing properties of his bile-cultivated attenuated tubercle bacilli are full of the most serious promise. It is not unreasonable to presume that the serum of animals powerfully immunized against tuberculosis may have curative virtues.

But whatever the remedy shall be, I feel confident that, as I said before concerning the air-and-rest cure, collapse therapy will not lose its rights. It holds the first rank now,—in the hope and expectation of something better still. When our hopes will be fulfilled, it will hold the second rank only, but as a most useful and often quite indispensable auxiliary. It will always be advisable to suppress the mechanical obstacles that stand in the way of healing, and to put the lung of the patient, as well as the patient himself, under the most favorable conditions for the specific treatment to do its work.

I am even inclined to imagine that artificial pneumothorax, the practice of which has put before us so many problems and has enriched to such a degree our knowledge of the physiology and pathology of the respiratory organs, may also very materially prepare the way for the longed-for specific treatment of tuberculosis. The careful and persevering observation of patients, gradually restored to health under the influence of artificial pneumothorax, gives us the best possible opportunity for studying those natural processes of healing which, after all, are probably the key to the discovery of a rational and specific therapy. What is more surprising, for instance, than the way a laryngeal tuberculosis heals spontaneously and without any local treatment in a patient whose pulmonary tuberculosis is being treated successfully by artificial pneumothorax? You have certainly noticed also the very remarkable and sudden change for good which sometimes follows the development of a serofibrinous exudate into the pneumothorax cavity. The sputum

rapidly diminishes and the tubercle bacilli disappear from it. And yet the X-ray examination does not demonstrate any noticeably increased collapse of the diseased lung in which a cavity may even remain patent; and the exudate itself may be exceedingly rich in tubercle bacilli. I have always thought that it would be worth-while to investigate those exudates from an immunological point of view. Recently one of my assistants, Dr. Veber of Bucarest, has undertaken in my laboratory some preliminary research work in that direction following my suggestions. He has been able to show that the bacilli which are found in such large quantities in some of those exudates are occassionally quite incapable of being cultivated. If living tubercle bacilli, taken from a well-growing culture, are put in contact for 24 hours with a filtrate of such an effusion in the incubator, and are then put to grow on glycerine-potato or on Petroff's medium, they will not grow, whereas on the control test-tubes bacilli taken from the same culture develop normally. Evidently, such exudates possess very remarkable inhibiting properties, which it is interesting to compare with the allergic phenomena, which Manwaring and Bronfenbrenner, Paterson, and myself in coöperation with Kindberg and Rolland, studied many years ago in the exudates determined by intraperitoneal and pleural reinfection of tuberculous guinea pigs.

I do not wish to draw any premature or far-reaching conclusion from such experiments. My object has been merely to give an instance out of many of the kind of problems which the practice of artificial pneumothorax may put before the scientific mind. Collapse therapy is not only the greatest advance which has been made in the treatment of tuberculosis. It has opened new ways to pathological and immunological investigation. Its study holds in reserve for us much more than its routine every-day practice seems to mean. With artificial pneumothorax a new era has begun.

RESULTS OF ARTIFICIAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS[1]

EDOUARD RIST[2]

I believe it is almost universally admitted to-day that artificial pneumothorax is the most remarkable advance made thus far in the treatment of pulmonary tuberculosis. It has considerably improved the prognosis of certain very common forms of consumption, which, before its advent, were regarded as nearly invariably hopeless. No competent physician would consent to be deprived of its services. But when it comes to measure the extent of those services and to substitute dry and matter-of-fact figures for the impressions derived from our personal experience, we find ourselves confronted by great difficulties.

Of course, there is no physician, who, having treated even only a small number of cases with artificial pneumothorax, cannot report about individual patients, who, doomed to certain death, recovered and were restored to health in a way, which, when the new method was first heard of, seemed quite extraordinary. On the other hand, there is no one who cannot tell of only partial or temporary successes and even of total failures. It is a common and dangerous delusion which inclines us to put in the foreground what seems extraordinary. *Extraordinary* is, plainly, synonymous with *exceptional.* A new therapeutic procedure, in order to be regarded as legitimate and as deserving to be recommended in every-day practice, has to give good proof that its successes are not extraordinary but ordinary. Figures only can supply this proof, and they ought to be large enough to carry conviction.

Furthermore, it is an absolute requirement that the cases which we tabulate should be of the same kind and order. The forms and aspects of chronic consumption are so manifold that it is far from easy to satisfy that requirement. Indeed one of the most serious problems which lies before us is to classify those forms. Among the several schemes of classification which have been proposed recently, there is none which

[1] Presented before the Clinical Section at the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 7, 1926.

[2] Co-Director, Tuberculosis Division, Laennec Hospital and Dispensary, Paris, France.

seems quite to the point, none which has succeeded in taking into account, in a really practical way, all the numerous and intricate factors implied, none which has obtained universal agreement so far.

At the present time, every one of us, even if he adheres to some more or less official scheme, interprets it in his personal way, and, for all practical purposes, has a kind of classification of his own, according to which he chooses his cases for artificial pneumothorax. But where are his controls? If he compares the fate of his treated patients with the fate of those whom he deemed unfit for collapse-therapy, he will be unable to prove anything. Shall he divide the patients whose condition, according to his judgment, requires artificial pneumothorax, into two groups, of which one will be treated and the other not? We may use such a strictly experimental method with guinea pigs but not with our fellow-men. And were we cold-blooded enough to try it, we could not do it correctly for psychological reasons: our choice would inevitably be biased by subconscious tendencies.

Fortunately—if I may say so—we are saved from the responsibility of a personal and arbitrary choice, and placed under conditions as nearly experimental as possible by the patients themselves. They fall spontaneously, and by their own accord, into the two groups which we need for our comparison, by either accepting or refusing treatment. In every dispensary, in every tuberculosis hospital-department, we meet a certain proportion of patients whom we regard as fit for artificial pneumothorax, and who stubbornly refuse such treatment. They are afraid of it, they have heard absurd tales about it, they are unwisely advised at home, they want first to try some fake medicine. Such are some of the reasons which prevent consumptives, not only among the ignorant but also among so called educated people, from being treated as they should be. We must, of course, do our very best to persuade them. But if they persistently refuse, we have a right to take, so to speak, advantage of their folly, and to put them down on the list of our controls. They will enable us to endeavor to make a statistical study of the net results of artificial pneumothorax on a sound basis. Our cases are selected for treatment according to our own judgment, without our knowing beforehand whether the patients will or will not submit to it. Among that practically uniform group, for reasons absolutely unconnected with any medical bias, the patients themselves decide who shall be treated and who shall not. I have made it a rule in my Department to keep track as thoroughly as possible of our refusals, to have them followed up by our

visiting nurses, to help and assist them no less carefully than those who followed willingly our advice. Of course, a large proportion of them escape without notice and do not let us hear of them any more. But we manage nevertheless to keep in touch with a number sufficient for our purpose.

There are also controls of a somewhat different kind, namely patients who have agreed to follow the physician's advice, but whose diseased lung was unable to be successfully collapsed on account of extensive pleural adhesions. Yet I am inclined to think that they do not represent a group quite as valuable for comparison as the aforementioned one. It is not altogether unlikely that, in a certain proportion of cases at least, complete adhesion of the pleural space goes hand in hand with a marked fibrotic tendency of the tuberculous process in the lung, and that therefore the prognosis of such cases, left to themselves, should be considered somewhat more favorably than if they had no adhesions. This is perhaps counterbalanced by the following consideration: namely, that the refusals, being generally unintelligent and of weak character, are likely to make their case still worse, whereas the patients who have accepted pneumothorax, and have been very much disappointed by its failure on account of adhesions, are more inclined to take good care of themselves and to submit to an air-and-rest cure in a sanatorium.

Having those guiding ideas in mind, I undertook, with the coöperation of my assistant, Dr. F. Hirschberg, to make a statistical survey of all the cases which I have treated personally or which have been treated under my supervision in my Department at the Laennec Hospital in Paris, from November, 1912, until January 1, 1926, the condition of the patients having been controlled up to April 1, 1926. I think I ought to mention that my Department, entirely specialized in pulmonary tuberculosis of the adult, consists of 200 beds, and that, connected with it and also under my personal direction, there is a large dispensary consultation service. The admittance of the patients to the wards is made exclusively through the dispensary. On the other hand, patients discharged from the wards are followed up by my visiting nurses and social workers and come back to my dispensary consultation. Patients with artificial pneumothorax are kept in the wards as long as possible, as a rule not less than three months, sometimes much more. Whenever it is feasible they are sent subsequently to a sanatorium, where the treatment is continued, and where they stay for a period which can hardly exceed six months.

Only a limited proportion of our cases, however, can have the benefit of sanatorium treatment, owing to the scarcity and congested state of our institutions. Therefore the greater number of our pneumothorax cases, after having been discharged from the wards, have their refills made at the Dispensary, where special days are reserved for that work, which always implies a fluoroscopic examination before and after each refill. The number of refills thus performed at my dispensary averages 3,500 a year. Of course such an organization has some very serious drawbacks. It requires a numerous personnel, whose term of office may be considerably shorter than the duration of treatment in an individual case; it is not possible to provide for each patient being always refilled and examined by the same interne or the same assistant. Furthermore, the newly appointed man who takes charge of a certain group of cases is inevitably less experienced and less skilful in this particular work than his predecessor who has done it for a year or more. The result is that treatments are not sufficiently individualized and that mistakes are made which are more easily avoided in private practice.

Another drawback is the fact that our patients, belonging mostly to the poorer part of the population, are too often driven by sheer necessity to begin work again, at a period of their treatment when they ought, on the contrary, to keep at rest.

In concluding these preliminary remarks, I wish to emphasize the fact that *all* the cases treated in my Department have been included in this survey. Therefore, the earlier cases date back to a period when neither my assistants nor myself had any experience in the method. In fact, we had to learn it. Some of those early cases may weigh a little heavily on the dark side of our statistics. Furthermore, a year and half after we had begun, the war broke out, thus diverting our medical activities into quite different channels. Many patients who were doing well have been lost track of during that period, and many were unable to have their treatment continued. This also must be taken into account.

The total number of patients submitted to artificial pneumothorax during that period of 13 years amounts to 1,009. I shall leave out of consideration the cases (42 in number), in which collapse was induced for nontuberculous disease, such as bronchiectasis or lung abscess. I shall also exclude tuberculous cases belonging to rather exceptional categories or deserving to be studied separately, namely, exudative pleurisy

converted into artificial hydropneumothorax (13 cases); spontaneous pneumothorax artificially maintained (16 cases); emergency artificial pneumothorax induced on account of uncontrollable haemoptysis (5 cases); acute pneumonic and bronchopneumonic forms (45 cases); bilateral tuberculosis (71 cases); and finally pneumothorax coincident with pregnancy (58 cases). Each one of these groups has interesting features, but the short time which is at my disposal makes it imperative that I should leave them outside of the present discussion.

We have therefore to deal only with 759 cases of chronic, common unilateral tuberculosis of the lung, the ordinary form of consumption, which after all concerns us most. All of them had bacilli in their sputum. All had an involvement of at least one-half of a lobe, and often of much more. Nearly all of them had one or several cavities, as ascertained by X-ray plates.

Of those 759 cases treated by artificial pneumothorax, 387 were clinically well at the close of our survey; they fall into a first group of 51, whose refills have been definitely interrupted, and a second group of 336 who are still under treatment. The proportion of cases who need no more refills appears to be small. But one must take into account that there are many patients who are very reluctant when it comes to putting a full stop to their treatment. They feel perfectly well. They have had no symptoms for many years. Their sputum, if they occasionally have any, is permanently free from bacilli and does not infect the guinea pig. They are able to work and lead a normal life. But they are aware that giving up the refills ultimately means permanent pleural adhesions, and therefore precludes the possibility of creating a pneumothorax anew, if a relapse should occur. They consequently much prefer to keep their once-diseased lung collapsed, even unnecessarily. I have found this particular state of mind very prevalent, at least among French patients. Conversely, it sometimes happens that the refills have to be given up much earlier than we would have desired, on account of spontaneously developed adhesions, either after a liquid effusion or without any such effusion. Eventually it, of course, leads to a recurrence of all the symptoms and to progressive extension of the disease. But there are also cases which turn out quite surprisingly well, as if the process of healing initiated by a temporary collapse went on despite its interruption. Tables 1, 2 and 3 detail these 51 cases according to time.

It is not an exaggeration to speak of complete healing in this group. Nevertheless, we must keep in mind that a relapse in the once-diseased

TABLE 1

Duration of continuous collapse

	cases
Less than 1 year	7
Over 1 year	10
Over 2 years	11
Over 3 years	7
Over 4 years	7
Over 5 years	5
Over 6 years	2
Over 7 years	2
Total	51

TABLE 2

Time elapsed since pneumothorax was induced

	cases
Over 1 year	2
Over 2 years	6
Over 3 years	6
Over 4 years	5
Over 5 years	10
Over 6 years	8
Over 7 years	3
Over 8 years	2
Over 9 years	2
Over 10 years	3
Over 11 years	2
Over 12 years	1
Over 14 years	1
Total	51

TABLE 3

Time elapsed since pneumothorax was interrupted

	cases
Under 1 year	7
Over 1 year	12
Over 2 years	11
Over 3 years	4
Over 4 years	3
Over 5 years	7
Over 6 years	4
Over 7 years	1
Over 10 years	2
Total	51

lung is not absolutely precluded. I have in my files 2 cases in which such a relapse occurred after a prolonged interval of apparently restored health; 4 other patients, also brought back to a normal condition, had a relapse in the contralateral lung: two of them ultimately died; the other two are still under treatment with contralateral pneumothorax.

The majority of our 387 successful cases, namely 336, are still under treatment. Some of them are without doubt definitely cured and could safely be left without refills; but, as I said before, they feel secure with their collapse and object to its being interrupted. The rest, if we discard their obligation of being periodically refilled, enjoy nearly all the

TABLE 4

Duration of artificial pneumothorax on April 1, 1926 (group of 336 well patients still under treatment)

	cases
Under 6 months	7
Over 6 months	51
Over 12 months	49
Over 18 months	52
Over 24 months	53
Over 30 months	36
Over 36 months	18
Over 42 months	20
Over 48 months	9
Over 54 months	18
Over 60 months	12
Over 66 months	9
Over 6 years	3
Over 7 years	4
Total	336

privileges of a normal condition of health. But the time elapsed since their pneumothorax was induced is not yet long enough to make us feel that anatomical healing has progressed at the same rate as functional healing. The patients of this group have neither cough nor expectoration. Their occasional sputum is permanently free from bacilli, as ascertained by guinea-pig inoculation; their temperature is normal; they gain weight. What is still more significant, they are able to work; and, as a matter of fact, the majority of them do work, earn their livelihood and support their families. Table 4 shows the duration of treatment so far, in this group.

Let us now turn to our unsuccessful cases. They number 372, and can be divided into 3 groups, namely, (1) condition unchanged, 33 cases; (2) development of contralateral lesions, 99 cases; (3) deceased, 240 cases.

In the group, *Condition Unchanged*, I have put the cases which do not seem to derive any marked benefit from the treatment, either because limited adhesions or the density and rigidity of the lung prevent an efficient collapse of the diseased part. Coughing, expectoration and temperature are not or are only moderately influenced. The sputum still contains bacilli. A certain proportion of such cases would be benefited by a thoracoplastic operation. I also added to this group the cases in which an inexhaustible and persistently recurring purulent exudate becomes fistulized through the chest-wall. They must not however be

TABLE 5

Time of onset of contralateral lesion

	cases
During first 6 months of treatment	139
From 7th to 12th month	53
From 13th to 18th month	34
From 19th to 24th month	8
After 2nd year	20
After 3d year	12
After 4th year	10
After 5th year	1
After 6th year	1
Total	278

regarded as absolutely hopeless. Some of them ultimately heal completely.

The cases which figure in the group, *Development of Contralateral Lesions*, represent, of course, a group which is constantly shifting. The development of contralateral lesions is by far the most frequent among the serious complications of artificial pneumothorax. It is responsible for 75 per cent of the deaths. When my figures were collected, we had 99 of such cases alive; but 179 more had died previously. The sum total is therefore 278. Table 5 shows the distribution of these cases according to time.

About 50 per cent of contralateral lesions occur during the first six months after artificial pneumothorax has been induced. The more time

that has elapsed since the beginning of treatment, the less chance there is that the sound lung should be involved. But of course there are a few cases of late contralateral lesions, and the margin of safety is rather elastic. During the first years of our experience, we invariably gave up the artificial-pneumothorax refills when contralateral lesions made their appearance; and the patient more or less slowly died. We know better now. The contralateral lesions may heal spontaneously, provided the collapse of the primarily affected side is kept up, and the patient put on absolute rest in bed. Or, else, if the collapse of the first diseased lung has lasted long enough to make its healing likely, one may have it discontinued and induce an artificial pneumothorax on the contralateral lung. And in some cases one may even attempt a bilateral collapse.

TABLE 6

Causes of death in 240 cases of artificial pneumothorax

	cases
Contralateral lesions	179
Perforation of the lung	18
Intestinal tuberculosis	10
Empyema	4
Generalized miliary tuberculosis	3
Tuberculous meningitis	3
Haemoptysis	3
Amyloid	2
Distention and failure of the heart	1
Pulmonary embolism after phlebitis	1
Adrenal tuberculosis	1
Unknown	15

There is therefore a certain though small proportion of cases in this group that may ultimately be transferred to the well group. But by far the greater number, I am afraid, will sooner or later pass on to the deceased. Furthermore, cases from the well group will have to be shifted into the contralateral group.

The total number of our deaths is 240. It is likely that this figure is somewhat too small: among the secondary bilateral cases, just mentioned, a certain number were certainly dead when our figures were tabulated; but we had not yet had a definite confirmation of the fact. The immediate causes of deaths are given in table 6.

It will be noticed that perforation of the lung is second in importance among the causes of death, but it comes a long way after bilateralization.

It is a rather early complication. Among our 18 cases, 12 occurred during the first five months of treatment, 5 after one year, and one after three years.

The net result of artificial pneumothorax in our 759 cases is shown in percentage in table 7.

Before we pass judgment on these results, which some of you may think very modest, let us inquire into the fate of our controls.

TABLE 7

Percentage of results in 759 cases of artificial pneumothorax

		per cent	
Healed	51	6.5	52 per cent
Clinically well, symptom-free, working, but still under treatment	336	45.5	
Condition unchanged	33	4.	48 per cent
Bilateral (alive)	99	13.5	
Deceased	240	30.5	
Total	759	100	100 per cent

TABLE 8

Condition of controls (adhesions)

		per cent	
Able to work	8	8.5	
Living in institutions (unable to work, condition unchanged or worse)	35	37.2	91.4 per cent
Deceased	51	54.2	

TABLE 9

Condition of controls (refusals)

		per cent
Condition unchanged	13	18
Worse	22	29
Deceased	39	53

During the period considered, we failed in our endeavor to produce an artificial pneumothorax on 250 patients, on account of extensive pleural adhesions. Therefore, on a total of 759 + 250 = 1,009 cases of unilateral consumption, approximately 1 in 4 has a blocked pleural space. We have lost sight of 156 of these 250 patients; but we have been able to follow up the remaining 94. Their condition on April 1, 1926, is shown in table 8.

Regarding the patients living in institutions and outside of our personal control, we have not had information sufficiently detailed to enable us to discriminate between those whose condition was unchanged and those who were getting worse. But we positively know that they are unable to work and still have bacilli in their sputum.

On the other hand, 213 patients, whom we considered fit for pneumothorax treatment, could not be persuaded to submit to it. We have been able to keep track of 74 of them. Their condition is shown in table 9.

If we compare the 30.5 per cent mortality of our treated cases with the 53 to 54.2 per cent mortality of our controls, there does not seem much reason for overenthusiasm. A more striking difference appears if, anticipating a little the near future of the patients who have become worse, we add them to the deceased. The group *worse* + *deceased* represents 44 per cent of the treated cases and 82 per cent of the refusals.

If we add the *unchanged* to the *worse and deceased*, this total group of *failures* represents 48 per cent of the treated cases, 91 per cent of the untreated on account of adhesions, and 100 per cent of the untreated on account of refusal.

But the comparison is still more illuminating if we consider the successful cases, as follows:

Whereas 6.5 per cent of the pneumothorax patients are healed anatomically as well as functionally, this group is not represented at all among the patients who have not been submitted to collapse-therapy, either because they had adhesions or because they refused treatment.

If we add those 6.5 per cent to the 45.5 per cent pneumothorax cases who are functionally healed and enjoy all the privileges of good health, including their capacity for work, we have a total of 52 per cent of well patients, leading a normal life and expectorating no bacilli, against 0 per cent among the refusals. Among the patients with adhesions making them unfit for pneumothorax, only 8 per cent are able to work, some still having bacilli in their sputum.

I have no doubt that still better results could be, and certainly will be, obtained in the near future. The earlier the patients are submitted to collapse-therapy, the more favorable will the outlook be. The profession at large has still to realize that artificial pneumothorax ought not to be unduly delayed. The technique of its application can be improved. The development of social service in our hospitals and dispensaries will enable us to have a closer control of our pneumothorax cases, and to help them efficiently, in order that they should not take up work too early.

But, taking our figures at their face value, I think they show that, notwithstanding its drawbacks and failures, notwithstanding the somewhat unfavorable conditions under which it is almost inevitably practised in hospitals and dispensaries, artificial pneumothorax is capable of doing what no other method has ever achieved. Its successes are limited, it is true. But, beyond any discussion, they are positively proved.

THE REACTIONS OF GUINEA PIGS TO GRADED CONJUNCTIVAL INFECTIONS WITH TUBERCLE BACILLI[1]

S. LYLE CUMMINS[2]

The experiments about to be described were undertaken with the hope of throwing some light upon the following points:

1: The effects of preinfecting doses of varying strength and virulence upon the toleration capacity of guinea pigs to a subsequent infection of standard strength and proved virulence.

2: The variations, if any, in the pathogenic sequence of clinical phenomena following infections and reinfections of guinea pigs with different amounts of tubercle bacilli introduced through a natural portal of entry.

For experiments of this nature, the conjunctival route of infection has certain advantages. This method of bringing about infection in laboratory animals was first employed by Calmette and his co-workers (1) in 1913 and, in a series of observations (2) carried out by the author in 1924, gave results which were regarded as promising. It may be claimed as a "natural" mode of entry of tubercle bacilli, since the germs are introduced without the creation of an artificial lesion, and are obliged to pass by natural channels instead of through traumatic apertures; and it appears to be better than the intestinal route since the varying factors depending upon differences in the volume and reaction of the gastric and intestinal contents and rapidity and energy of peristaltic gut movements are avoided.

It has been found by the author that a volume of 0.01 cc. of fluid can be instilled into the conjunctival sac of the guinea pig without subsequent overflow, and this volume has been used in all the experiments carried out. Doubtless, these instillations are got rid of by the same channels

[1] Presented at a Session on *Immunization* before the Pathological Section of the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 4, 1926.

[2] David Davies Professor of Tuberculosis, University of Wales, Cardiff, Wales.

as the lachrymal fluid; in fact, it can be seen that the amount of fluid rapidly diminishes after the drop has been introduced: but, even if much of the instillation passes away along the lachrymal duct and enters the nose, it still remains in contact with a mucous membrane; and the sequence of events may be assumed to vary but little as between one animal and another.

In practice, it is found that the effects of standard doses of infective germs thus introduced are fairly comparable in uninfected guinea pigs of approximately similar age and weight; a fact which recommends the method for work in which "control" observations are required.

From the point of view of study of clinical sequelae, the conjunctival route has obvious advantages, since the subsequent phenomena at the point of entry and in the neighboring lymph nodes can be seen or palpated at any time during the course of the experiment.

On February 15, 1924, fourteen healthy guinea pigs were chosen and separated into two groups of 7 animals each.

At the same time, two egg-medium cultures of human tubercle bacilli were selected, the one (*T. B. 100*) an old laboratory strain obtained from Captain S. R. Douglas, F. R. S., of the National Research Laboratory, Medical Research Council; the other, *T. B. Richards*, a virulent strain isolated by the author from an acute case of advanced pulmonary tuberculosis. Douglas's strain has proved, in observations at Cardiff, to be of very low virulence for guinea pigs. These cultures, both aged about four weeks, were made into homogeneous emulsions by means of the Hadyn mortar, and standardized so that each emulsion corresponded with an opacity of *number 5* on Brown's Scale (3), found, in the course of several "counts" by the author, to represent about 5,000 million tubercle bacilli per cubic centimetre.

Each of these bacillary emulsions was now diluted in tenths, so as to obtain a series of seven concentrations varying from one-tenth to one ten-millionth of the original emulsion. With a graduated pipette, a volume of 0.01 cc. of each dilution was now instilled into the conjunctival sac of each guinea pig, one group of 7, group A, receiving the attenuated strain, the other, group B, the virulent strain. Details of these groups and the individual doses administered are given below, as follows:

		bacilli
Group A:		
Guinea pig 268.	Preinfecting Dose	5
269.		50
270.		500
271.		5,000
272.		50,000
273.		500,000
274.		5,000,000
Group B:		
Guinea pig 261.	Preinfecting Dose	5
262.		50
263.		500
264.		5,000
265.		50,000
266.		500,000
267.		5,000,000

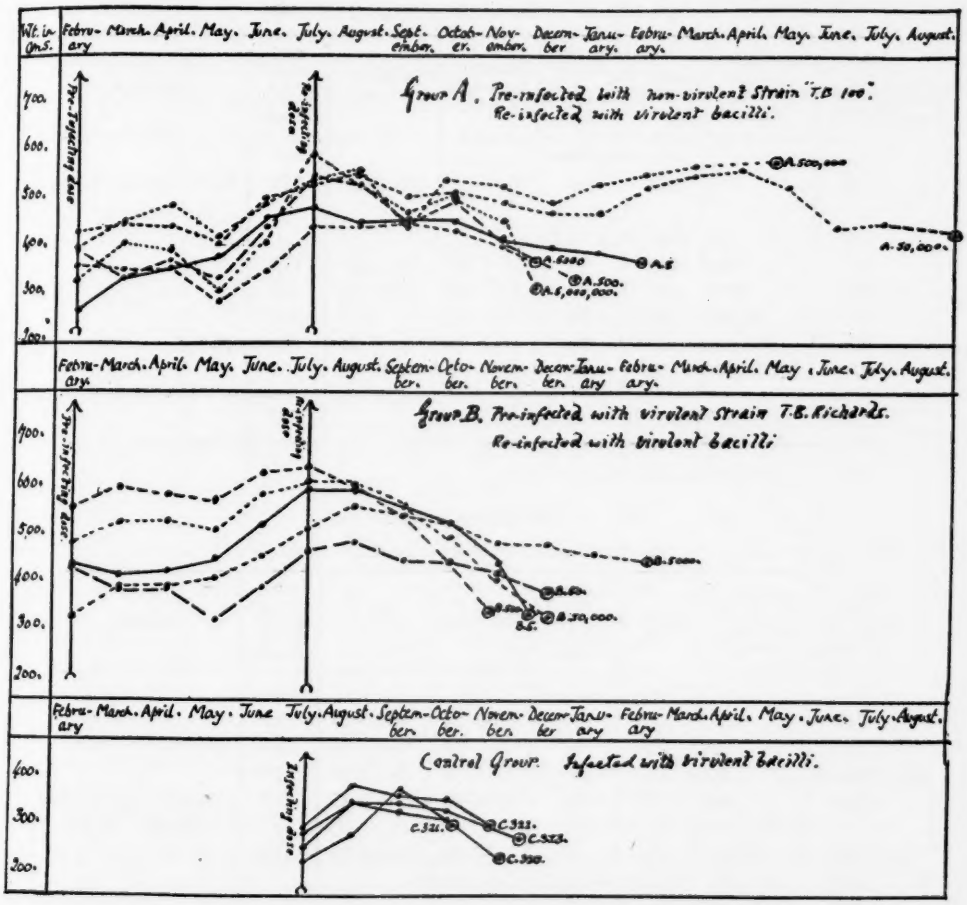
One guinea pig, no. 269 of group A, died of an intercurrent disease on February 24, 1924. At autopsy there were no visible signs of tuberculosis. A lymph node, removed from the cervical region on the left side, was emulsified in saline solution, and inoculated into a healthy guinea pig subcutaneously. This animal died some three months later from tuberculosis, suggesting that some of the bacilli from the conjunctival instillation had reached cervical lymph nodes within thirteen days. Unfortunately, there is just a shade of doubt as, through the breaking of a shelf, the test-animal, along with others, escaped from its cage; but there is every reason to feel assured that the animals were rightly sorted, and it seems worth while to mention the result.

None of the remaining animals were lost through intercurrent disease.

The clinical events in these animals will be considered later. Here it will suffice to say that the two guinea pigs receiving the strongest dose of the virulent strain, nos. 266 and 267, died of generalized tuberculosis on May 9, 1924, eighty-three days after their initial infections, their deaths being, perhaps, expedited by a tuberculin test applied alike to all the group animals on April 28, 1924; but both these guinea pigs were showing signs of heavy infection before the test, consisting of an intracutaneous inoculation of 0.1 cc. of a 1 to 50 dilution of old tuberculin, was carried out. By the first week of July, 1924, the 6 survivors of group A and the 5 survivors of group B had all recovered from such transitory signs and

symptoms of infection as had at first developed, and were, seemingly, in good health.

A further tuberculin test, applied on July 3, was negative in guinea pigs 261, 262, 263, 264 and 274, doubtful in 268, and slightly positive in the rest.



GRAPH 1. WEIGHTS AND SURVIVAL PERIODS OF GROUPS A AND B, AND CONTROL GROUP

With these animals it was now possible to test the effects of a further dose of virulent tubercle bacilli, and it was decided to employ a standard dose of 50 million of the culture already used, *T. B. Richards*, of which a dose of 500,000 had proved lethal for guinea pig 266.

To this end, a fresh emulsion of *T. B. Richards* was prepared, in every

respect comparable to that used on the previous occasion and, without dilution, a volume of 0.01 cc., or approximately 50 million bacilli, was instilled into the left conjunctiva of each of the surviving guinea pigs of

TABLE 1

Preinfected group A

Preinfected with Attenuated Strain T. B. 100

GUINEA PIG SERIAL NUMBER	PREINFECTING DOSE (CONJUNCTIVAL)	INTERVAL	VIRULENT INFECTING DOSE (CONJUNCTIVAL)	DATE OF INFECTING DOSE	DATE OF DEATH	SURVIVAL AFTER INFECTING DOSE	REMARKS
		days	*millions*			*days*	
268	5	150	50	15–7–24	14– 2–25	214	Death accelerated by further dose
269	50	Died after 10 days					
270	500	150	50	15–7–24	1– 1–25	170	
271	5000	150	50	15–7–24	5–12–25	150	
272	50,000	150	50	15–7–24	30– 8–25	*411*	
273	500,000	150	50	17–7–24	7– 5–25	*296*	Killed
274	5,000,000	150	50	17–7–24	8–12–25	153	
Mean time of survival.....						*232*	

TABLE 2

Preinfected group B

Preinfected with Virulent Strain T. B. Richards

GUINEA PIG SERIAL NUMBER	PREINFECTING DOSE (CONJUNCTIVAL)	INTERVAL	VIRULENT INFECTING DOSE (CONJUNCTIVAL)	DATE OF INFECTING DOSE	DATE OF DEATH	SURVIVAL AFTER INFECTING DOSE	REMARKS
		days	*millions*			*days*	
261	5	150	50	15–7–24	4–12–24	140	
262	50	150	50	15–7–24	17–12–24	153	
263	500	150	50	15–7–24	8–11–24	119	
264	5000	150	50	15–7–24	19– 2–25	*219*	Death accelerated by further dose
265	50,000	150	50	15–7–24	15–12–24	151	
266	500,000	Died 9–5–24 after Tuberculin					
267	5,000,000	Died 9–5–24 after Tuberculin					
Mean time of survival.....						*156*	

groups A and B. At the same time a third series of 4 animals, guinea pigs 320, 321, 322 and 323, were chosen as controls, and were infected in the same manner, receiving 50 million bacilli *per conjunctivam*, this last series being called *group C*.

All these instillations were carried out on July 15, 1924, and the subsequent events, so far as weight and survival period are concerned, are shown in graph 1.

For convenience of reference, the dates of preinfection, reinfection and death of each animal are set forth in tables 1, 2 and 3; table 3, dealing with controls, being supplemented by the addition of 7 other guinea pigs since infected, in the course of other experiments, with the same dose of the same strain instilled in the same manner.

Apart from clinical phenomena, the only criterion we can apply in the

TABLE 3

Control group C

Infection with Virulent Strain T. B. Richards

GUINEA PIG SERIAL NUMBER	VIRULENT INFECTING DOSE (CONJUNCTIVAL)	DATE OF INFECTING DOSE	DATE OF DEATH	SURVIVAL AFTER INFECTING DOSE	REMARKS
	millions			*days*	
320	50	15- 7-24	21-11-24	129	Original control group
321	50	15- 7-24	21-10-24	98	
322	50	15- 7-24	12-11-24	120	
323	50	15- 7-24	30-11-24	138	
553	50	8-12-25	5- 5-26	148	Control group to a later experiment
554	50	8-12-25	21- 3-26	103	
555	50	8-12-25	6- 4-26	119	
556	50	8-12-25	15- 3-26	97	
567	50	21-12-25	8- 4-26	108	Control group to sanocrysin experiment
568	50	21-12-25	18- 3-26	87	
570	50	21-12-25	22- 4-26	122	
Mean survival period.....				*115*	

evaluation of resistance to the reinfecting dose is the period of survival as compared to that of the controls. It is to be regretted that this factor was not sufficiently appreciated at first, and it was decided to regard the experiment as finished, and to round off the observations six months after the date of reinfection. Acting on this idea, the unfortunate decision was taken to employ guinea pigs 264 of group B and 268 of group A for another experiment when they had overpassed their six-month period. They were chosen as obviously infected animals with definite symptoms, and were given large intracutaneous injections of living tubercle bacilli in connection with some experiments on Sanocrysin.

Both died in the third week of February, 1925, having survived their conjunctival reinfection by seven months. Both would, in all probability, have died before long, but it is safe to assume that their survival period was shortened by the further infection induced in January, 1925. In the case of guinea pig 273 of group A, it was thought advisable to kill and examine this animal on May 7, 1925, at a time when the disease had apparently come to a state of quiescence. From the very chronic and fibrous nature of the lesions found at the autopsy, it may be assumed that this guinea pig would have survived at least as long as guinea pig 272, which was allowed to reach a natural end. These interferences with the course of the initial experiment are mentioned, to show that the average survival periods in groups A and B, as indicated in tables 1 and 2, are underestimates, a fact which should be borne in mind in attempting to interpret them.

The salient facts, as indicated in these graphs and tables, are as follows: The mean survival period in 11 control animals was 115 days, the maximum being 148 days and the minimum 87 days. The mean survival period in group A was 232 days, a period which would unquestionably have been much longer if guinea pig 296 had not been killed. The maximum was 411 days and the minimum 150 days, the minimum being greater than the maximum survival in the control group. These findings must be taken to indicate that the preinfections in group A had had a definite effect in augmenting the toleration capacity of the animals to a lethal reinfecting dose.

In group B, however, the mean survival period was only six weeks longer than in the control group, and the findings are less significant. Here too the unfortunate interference with the results, due to the employment of guinea pig 264 for another experiment, has to be taken into account; and it is certain that the survival period of this animal would have been longer and would have raised the average as compared to the controls. But it seems clear that the toleration capacity of group B, even if greater than the controls, is definitely less than that of group A, the group in which the preinfections were from a nonvirulent strain.

A point of great interest comes to light when the relation of the size of the preinfecting dose to the period of survival is considered. It will be recalled that, in the original preinfecting part of the experiment, it was found that a dose of 500,000 bacilli of *T. B. Richards* led to the death of guinea pig 266, while a dose of 5 million bacilli of *T. B. 100* failed to lead to death in guinea pig 274. It may be inferred, then, that

the *infective potential* of *T. B. Richards* for normal guinea pigs was from ten to a hundred times as great as that of *T. B. 100*.

This finding lends a peculiar significance to the fact that the preinfecting doses associated with the longest survival in group A were 50,000 and 500,000 bacilli of *T. B. 100*, ten and one hundred times the optimum dose, 5,000 bacilli of *T. B. Richards*, in group A. With the possible exception of guinea pig 268, it appears that the animals preinfected with the smaller doses, in both groups, evinced but little increase of toleration capacity; while the same thing was true of those receiving very large preinfecting doses.

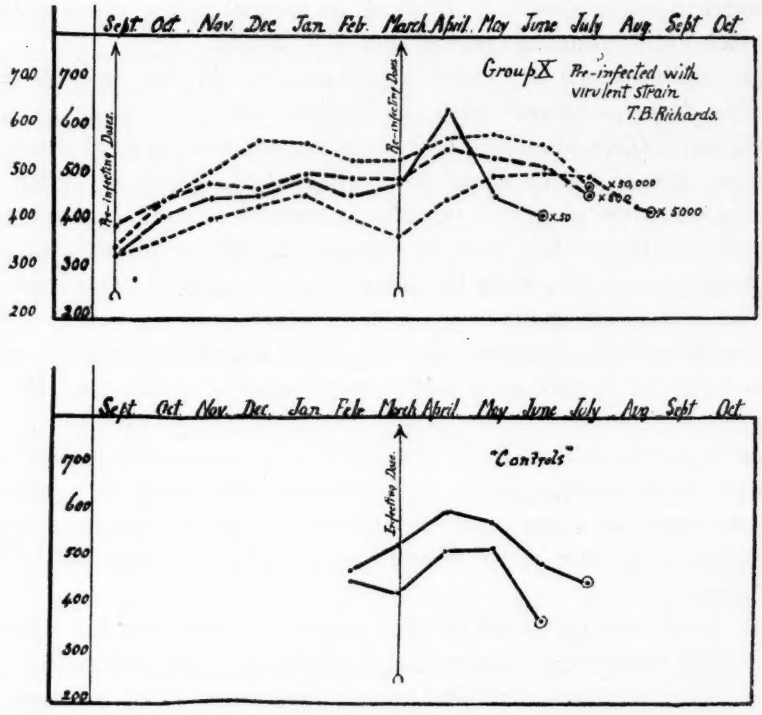
These observations suggest that very slight infections cannot be relied on as sufficient to produce a satisfactory degree of resistance. On the other hand, it seems that too heavy infections tend to establish foci of disease so severe as to be liable to activation by subsequent reinfections. Between these extremes, so far as the limited observations here recorded are concerned, lies a zone of preinfective dosage, which appears to induce a significant increase in the toleration capacity for subsequent lethal infections.

The mean survival period for the 3 guinea pigs, nos. 264, 272, and 273, preinfected with doses falling within the optimum zone, amounted to 342 days; and it is to be noted that two of these animals were brought to a premature end, the one by being killed for autopsy, the other by being used for a further experiment.

In view of this finding, it was clearly desirable to repeat the experiment. For this purpose, 4 guinea pigs were preinfected with serial doses of *T. B. Richards* on September 9, 1925, as follows:

Group X:		*bacilli*
Guinea pig 508.	Preinfecting Dose	50
509.		500
510.		5,000
511.		50,000

The results of this experiment are given in graph 2 and in table 4, a small control group being included. The interval between the preinfecting and the reinfecting dose was, on this occasion, longer than in the previous experiment, a period of 173 as compared with 150 days; and perhaps this may be the explanation of the shorter survival of the animals. The



GRAPH 2. WEIGHTS AND SURVIVAL PERIODS OF GROUP X AND ITS CONTROLS

TABLE 4

Preinfected group X

Preinfected with Virulent Strain T. B. Richards

GUINEA PIG SERIAL NUMBER	PREINFECTING DOSE (CONJUNCTIVAL)	INTERVAL	REINFECTING DOSE	DATE OF REINFECTING DOSE	DATE OE DEATH	SURVIVAL AFTER REINFECTING DOSE	REMARKS
		days	*millions*			*days*	
508	50	173	50	16–3–26	24–6–26	100	Died of tuberculosis
509	500	173	50	16–3–26	21–7–26	127	Died of tuberculosis
510	5,000	173	50	16–3–26	25–8–26	*162*	Died of tuberculosis
511	50,000	173	50	16–3–26	26–7–26	132	Died of tuberculosis
Mean survival period.....						*130*	

guinea pigs receiving the smaller and the largest doses are all dead, as are the controls. As in the previous experiment, in which *T. B. Richards* was used for preinfection, the animal receiving a dose of 5,000 bacilli

has outlived all the others, and still survives on the date of writing, 156 days after the reinfecting dose. (This animal died on August 24, 1926, a survival period of 163 days.)

All who have worked with guinea pigs in the investigation of tuberculosis are aware of the limitations of these animals for the purpose. But, while a much larger series of experiments is needed to settle the question, the results now recorded suffice to suggest the existence of a "zone of optimum preinfection" as a factor in the production of a satisfactory toleration capacity to reinfection. The bearing of this suggestion upon the problems of human tuberculosis is obvious.

VARIATIONS IN CLINICAL PHENOMENA FOLLOWING GRADED CONJUNCTIVAL INFECTIONS

The method of infection by conjunctival instillation is exceedingly convenient for the study of the pathogenesis of tuberculosis because the investigator has, under his direct observation, both the site of entry of the tubercle bacilli and also the neighbouring lymph nodes. This advantage was fully appreciated by Calmette, the first to use the method, who based upon it one of his arguments against the "Law of Parrot" and the similar views of Küss, Albrecht, Ghon, Canti and others.

Parrot's Law, *la loi des adénopathies similaires*, is summed up in the following phrase; "Whenever a bronchial lymph node is the site of a tuberculous lesion, there is a corresponding lesion in the lung."

Calmette has questioned the accuracy of this view and regards the lymph-node lesion as primary and the lung lesion as secondary. To quote his own words,

> La constatation de l'absence habituelle de toute lésion du poumon dans l'adénopathie trachéo-bronchique expérimentalement realisée par l'instillation de cultures ou de crachats bacilliferes sur la muqueuse saine de l'oeil chez les animaux sacrifiés de trois a quatre semaines après l'infection—tandis que si l'on attend davantage des tubercules identiques aux pretendus châncres d'inoculation de Parrot apparaissent, isolés ou solitaires, a la surface du poumon,—attestent que ces derniers ne sont que des manifestations secondaires de la tuberculose dite primitive des ganglions du hile.

The writer (4), in 1922, expressed his conception of "lesions of primary localization," regarding as primary all initial lesions situated in the area comprising the portal of entry, the neighboring lymph nodes and the

lymphatic channels joining the two, and it would seem from a paper by Anton Ghon (5), who does not, however, give the reference, that a similar conception had previously and much more authoritatively been enunciated by Ranke. It was with the idea of making a further study of this question that the writer, in 1923, applied Calmette's method and obtained results, already referred to, which appeared as a preliminary note in *Tubercle* in January, 1924.

These results appeared to be worth following up and the present paper is an attempt to summarize further work in the same direction.

Calmette, in applying his observations on perconjunctival infection of guinea pigs to support his argument against the validity of the Law of Parrot, attached much importance to the absence, in all his experiments, of any signs of lesion at the level of the eye itself. He invariably found that the first lesions to be noted were in the cervical lymph nodes, and he argued from this finding that these lymph-node lesions were to be regarded as "primary" in the strict sense of the word; with the implication that, in human infections, the tracheobronchial infections, so commonly found in children, were "primary" in the same sense, and the associated lung lesions recorded by Parrot, Küss, Ghon and others, "secondary," probably resulting from infection through the blood-stream.

In my own experiments, however, I found that eye symptoms tended to occur in the majority of the animals infected by the conjunctival route; an observation which afforded a sharp contrast with the findings of Calmette, and seemed to raise the question of whether his arguments against the Law of Parrot were adequate.

In the paper previously referred to, I discussed the question of whether the lesions described by me, of which photographs were published, were actually tuberculous or not, and I came to the provisional conclusion that they were tuberculous. The accuracy of this conclusion was confirmed, at a date subsequent to the appearance of the paper, by the finding of tubercle bacilli in sections of the affected eyes; and it may be added that, in the further experiments now referred to, inoculation of the eye discharges and even of the much less common nasal discharges of conjunctivally infected guinea pigs into fresh animals gave rise to tuberculosis in the latter.

There can be no doubt, therefore, as to the tuberculous nature of the eye lesions following conjunctival instillation of tubercle bacilli.

It had been found, however, in my preliminary experiments, that the lymph-node lesions were palpable some time before the eye inflammation

appeared; and so it became a question whether the adenitis was not primary, as suggested by Calmette, and the eye lesions secondary. The question, too, of the bearing of previous infection upon the time of appearance of the eye and lymph-node lesions, respectively, was raised by the fact that in one of two previously infected guinea pigs, in which conjunctival instillations were applied by me, the result was a very early appearance of eye inflammation, the animal dying of the earlier infection before any signs of cervical adenitis were noted.

The points to be settled by further experiment, therefore, were as follows:

1: What is the relation, in point of time, between the appearance of lymph-node lesions and eye lesions?

2: Is this relation altered through the hypersensitiveness resulting from previous tuberculous infection?

Considerable light was thrown upon the first of these questions by the results of the preinfecting instillations applied to groups A and B on February 15, 1924, but several points remained to be settled, and it was hoped to obtain further information through observing the sequence of events following the reinfections of these groups with a much larger dose of bacilli initiated on July 15, 1924. It was obviously necessary, too, to include a further group of animals, already infected with tuberculosis, so as to investigate the second of the questions at issue. By September 1, 1924, I was enabled, through the kindness of my colleague, Dr. Tytler, to employ for this purpose a group of 10 animals previously infected at dates not too remote, by the subcutaneous inoculation of pathological materials sent to the laboratory for investigation. In all these animals, there were already the signs of actual infection, in the shape of inflammatory thickening and lymph-node enlargement close to the sites of inoculation in the inguinal region. This series of animals, to be described as group D, was reinfected on September 1, 1924, by the conjunctival instillation of about 50 million tubercle bacilli in a manner exactly comparable to that employed in groups A, B and C.

To these four groups must be added group X, a series of four animals treated, as from September 24, 1925, in exactly the same manner as the animals of group B above described, and group Y, started on the same day as group X, and given not one, but a series of eleven preinfecting doses of the same strengths as those given to group X, these successive doses being spaced at weekly intervals. From the point of view of

clinical phenomena, therefore, there are six groups of guinea pigs to consider; but it will be best to commence with a general consideration of a few main points.

Eye Lesions

When eye lesions develop, the sequence of events is usually as follows:

From fourteen to fifty days or longer after the conjunctival instillation of germs, the interval varying under circumstances to be discussed later, the infected eye becomes moist as compared to the normal eye, and the degree of moisture rapidly increases, changing gradually from a clear tear-like fluid to a viscid and finally purulent discharge.

In many cases a marginal ulcer develops, usually in the upper and posterior quadrant of the corneoscleral junction, but more upon the scleral than the corneal part. This ulcer forcibly recalls the phlyctenular ulcers seen in children and is probably of the same nature. It shows a definite tendency to heal after lasting a few weeks. Whether an ulcer develops or not, the lids almost invariably show changes about this time, becoming thickened and inflamed, while the palpebral aperture becomes markedly narrowed. It is common to find, after the infected eye has shown signs of tuberculosis for some weeks, that the opposite eye becomes infected, doubtless as a result of transfer of discharge on the paws or by other means from the originally infected eye. While attempts to find tubercle bacilli in films from the discharge have not as yet succeeded, the inoculation of the discharge into another guinea pig gives rise to infection in the latter; and the same is true of the nasal discharge which has occurred in a few of the more severely infected animals; so there is no difficulty in explaining the secondary infection of the opposite eye.

One of the most remarkable features of these eye lesions is their tendency to become chronic and to show evidence of healing. In animals surviving long enough to allow of this amelioration, it is frequent to find fluctuations, the eye being practically normal at times and the inflammatory phenomena recurring for a day or two, only to disappear again the following week.

As the animal fails in strength, it is common to find the lids glued together with secretion and the eye completely closed. On forcing the lids apart, accumulated secretions escape and the eye often improves in the following days. In some of the animals, the eye inflammation stops short at the stage of increased lachrymation or completely recovers.

The histological changes in these tuberculous eyes require a much fuller study than has yet been possible. So far, the sections examined have shown areas of granulomatous infiltration, with sparsely distributed tubercle bacilli, in the scleral and submucous tissues around the orbit, but no lesions of the choroid or retina have been observed. No tubercles have been noted in the lachrymal gland. In a guinea pig, in which nasal discharge had occurred and had proved infective for a fresh animal, sections of the nasal mucous membrane were searched in vain for signs of tuberculous infection, but it must be added that the sections were not very satisfactory. Material for a more extended study has been preserved, and it is hoped to return to this question of histology at a future date.

Cervical Lymph-Node Lesions

The cervical lymph nodes usually become palpable within a fortnight or three weeks after the conjunctival instillation of tubercle bacilli. At first they are confined to the side corresponding to the instillation, but later affect both sides of the neck. The first nodes to be palpable are usually those placed rather superficially at the level of the posterior third of the ramus of the jaw. Then the small nodes in the angle behind the symphysis of the jaws become enlarged, and other nodes are soon appreciable in the cervical soft tissues. At autopsy, there seem to be four groups of nodes showing infection, a group of about four superficial nodes in the mental angle, a group of two or three larger superficial nodes on each side along the ramus of the maxilla, a group of several deep nodes, seldom large, along either side of the vertebral column in the neck; and one or two subauricular nodes, often markedly enlarged, which, owing to their being outside the angle of the jaw, may be missed at autopsy if not specially looked for. There is a salivary gland of considerable size under the middle third of the ramus on each side, which may be mistaken for a lymph node unless carefully examined. Its lobular structure indicates its true nature even to the naked eye.

In nonimmunized guinea pigs infected with large doses, these lymph nodes tend to become not only enlarged but caseous at an early stage. If the animals survive up to the end of the third month, the nodes may become very large; and the weight of the cervical lymph nodes has been found on two occasions to exceed three grams after drying for twenty hours on an absorbent slab.

In the animals preinfected with small doses, a tendency to recovery

after the original infection was invariably noted, and the lymph nodes had quite ceased to be palpable before the second dose was given. In some of the preinfected animals too, the lymph-node enlargements following reinfection have shown a definite tendency to recovery.

The rapidity with which enlargement of the nodes on the opposite side of the neck from the infected eye follows the earlier enlargements of the nodes on the infected side may possibly depend upon free communication by lymphatic channels across the neck, but may just as well be due to the accidental infection of the opposite eye. On this point, more information is needed.

Respective Priority of Eye and Lymph-Node Lesions

Before attempting to discuss this point, it is desirable to revert to the second question above postulated, as to whether the hypersensitiveness resulting from previous infection is capable of leading to early eye symptoms. The answer to this question appears, so far as my experiments have gone, to be in the negative. A freshly made suspension of washed tubercle bacilli differs from a dose of tuberculin in having but little bacillary substance in solution, and it does not usually give rise to reactions comparable to Calmette's ophthalmo-reaction. Neither in groups A, B, X or Y, nor in the group of infected guinea pigs described as group D, was any immediate inflammatory reaction noted in the eyes on reinfection by the conjunctival instillation of a large virulent dose. At this point, I wish to define a conception which has helped me to express to myself a factor in the train of events following the graded infections of animals with tubercle bacilli. It is convenient to speak of the *infective potential* of a given dose of tubercle bacilli for a given animal, in the sense that a small dose of virulent bacilli may be regarded as having the same infective potential as a larger dose of less virulent germs, while a standard dose of a standard strain may have a higher infective potential for a young or a nonimmunized animal than for an older or a preimmunized animal.

My experiments lead me to the conclusion that on the infective potential of the conjunctival instillation depends the priority of eye or lymph-node lesions respectively. When the infective potential is high, the eye and node lesions appear simultaneously, or the eye symptoms may even precede the adenitis. When the infective potential is relatively low, the node enlargement is always palpable before the eye symptoms ap-

TABLE 5

The time of appearance of lesions of eyes and lymph nodes in animals infected and reinfected with attenuated bacilli

Group A (Attenuated Strain T. B. 100)

GUINEA PIG NUMBER	FIRST DOSE	FIRST SYMPTOM	INTERVAL UP TO FIRST SYMPTOM	SECOND DOSE VIRULENT STRAIN	FIRST SYMPTOM	INTERVAL UP TO FIRST SYMPTOM
			days	*millions*		*days*
268	5	●	73	50	○	28
269	50	Died of intercurrent disease				
270	500	●	?	50	○	13
271	5000	●	51	50	○	17
272	50,000	●	31	50	●	42
273	500,000	●	19	50	⊙	30
274	5,000,000	●	31	50	⊙	30

● Gland inflamed. ○ Eye inflamed. ⊙ Eye and gland inflamed.

TABLE 6

The time of appearance of lesions of eyes and lymph nodes in animals infected and reinfected with virulent bacilli

Group B (Virulent Strain T. B. Richards)

GUINEA PIG NUMBER	FIRST DOSE	FIRST SYMPTOM	INTERVAL UP TO FIRST SYMPTOM	SECOND DOSE VIRULENT STRAIN	FIRST SYMPTOM	INTERVAL UP TO FIRST SYMPTOM
			days	*millions*		*days*
261	5	●	80	50	○	14
262	50	●	94	50	○	14
263	500	●	45	50	○	17
264	5000	●	52	50	○	14
265	50,000	●	38	50	○	14
266	500,000	●	19	Died of first dose		
267	5,000,000	⊙	19	Died of first dose		

● Gland inflamed. ○ Eye inflamed. ⊙ Gland and eye inflamed.

TABLE 7

The time of appearance of lesions in control animals

Cf with tables 5 and 6

Group C (control group)

GUINEA PIG NUMBER	INFECTING DOSE VIRULENT STRAIN	FIRST SYMPTOM	INTERVAL TO FIRST SYMPTOM
	millions		*days*
320	50	○	17
321	50	○	17
322	50	○	17
323	50	⊙	30

pear. Further, the lower the infective potential, the longer the interval of time before the adenitis or the conjunctivitis appears. These points are well brought out in tables 5, 6 and 7, illustrating the order of priority of eye and lymph-node lesions in groups A, B and C.

It will be seen from the tables that, in the case of the preinfections carried out in February, 1924, the adenitis was the first symptom in all the animals except guinea pig 267, in which eye and lymph node were simultaneously affected. This animal was the one which received the largest dose of the most virulent strain or, in other words, the dose with the highest infective potential.

In the case of the reinfections given to these animals in July, 1924, the only guinea pig in which the adenitis preceded the eye lesions was no. 272 of group A, the very animal which proved later, by surviving for 411 days, to be the most resistant of the lot; so that, for this animal, the infective potential of the standard dose of 50 million virulent bacilli was relatively low. In guinea pigs 273 and 274, both preinfected with the larger doses of a nonvirulent strain, and one of which proved extremely resistant to reinfection, the eye and lymph-node symptoms appeared simultaneously. In all the others of both test groups and the control group the eye symptoms preceded the lymph-node symptoms except in the case of guinea pig 323 of the control group, in which the eye and lymph-node symptoms appeared at the same time. It is to be noted that this animal outlived all the others of the control group.

In group D, in which all the animals had already evinced signs of infection as the result of subcutaneous inoculation with tuberculous materials or secretions, the considerable degree of resistance thus acquired sufficed to lower very definitely the infective potential of the standard reinfecting dose, with the result that neither adenitis nor eye lesions occurred to an extent comparable to the other groups. Of the ten animals in this group, one died of the original infection within three days of the reinfecting dose; it may therefore be ignored. Two others died of the initial infection within five weeks of reinfection. In neither was there any sign of cervical adenitis or conjunctivitis. It is possible, however, that eye or lymph-node symptoms might have appeared later had the animals survived. Of the remaining 7 animals, surviving from a minimum of 60 to a maximum of 216 days after reinfection, 3 remained quite free from palpable cervical lymph nodes, in 3 the presence or absence of enlarged cervical glands was recorded as doubtful, and in one only were the neck lymph nodes definitely affected both on palpation and at autopsy.

The contrast in the average weight of cervical lymph nodes removed postmortem and weighed under standard conditions is marked as between group D and the other groups, as may be seen in table 8; and it is of interest to observe how effective this preinfection by the subcutaneous route proved to be in comparison with perconjunctival instillation.

It should, however, be added that in two animals of this group, D, a low form of conjunctivitis was noticed some time after reinfection, precedent to the lymph-node enlargement, a finding not quite in line with what was noted in the other groups, and pointing to the possibility that other factors may require to be taken into account in relation to priority of eye and lymph-node lesions. This conjunctivitis never got beyond the stage of "wet eye."

In the case of group Y, in which the animals were given weekly doses of the same strength as those given, on the one occasion only, to group X,

TABLE 8

Average weight of cervical glands after death

	grams
Group A (5 animals)	1.43
Group B (3 animals)	2.16
Group C (3 animals)	1.66
Group D (5 animals)	0.34

The glands were dried on an absorbent tile over night at 37°C. and then weighed.

there was, with one exception, no development of either eye or lymph-node lesions during or subsequent to the course of eleven conjunctival instillations. The only exception was guinea pig 502, the animal to which successive doses of 5,000 bacilli were given. After the fourth dose instilled into the left eye, it was noticed that this eye became slightly inflamed and that a small corneoscleral ulcer developed. The remaining five doses were instilled into the right eye, and were followed by no symptoms. The left eye rapidly cleared up and became normal in appearance. In none of the group animals did adenitis appear after or during the preliminary course of instillations. Only two of the group survived long enough to permit of adequate observation after reinfection. In one of these animals, no. 502 already referred to, the lymph nodes became enlarged before eye lesions developed. In the other, no. 500, to which successive doses of 50 bacilli were given, eye and lymph-node symptoms

appeared simultaneously, 34 days after the reinfecting dose of 50 million germs.

Both these animals died from tuberculosis and, while the disease was of a fairly chronic type in both, they did not appear to be any more resistant than those of group X. On the whole, the effects of repeated preinfecting doses were, apparently, to lead to a state of ill-health, but not to produce any more resistance than the single dose.

The bearing of all these observations upon Parrot's Law may be considered at this point. Assuming that the conjunctival mucous membrane, its associated lymphatic drainage channels and the cervical glandular filters are comparable to the lung parenchyma, its lymphatics and the tracheobronchial and mediastinal lymph nodes, the experiments suggest that the fundamental factor upon which priority of lesion-site depends will be the infection potential of the dose or doses of tubercle bacilli leading to the lesion. If an infant or young child is subjected to heavy infection, it may be expected that the pulmonary lesion will precede or be simultaneous with the tracheobronchial adenitis, as postulated in Parrot's Law. If, on the other hand, the infecting dose is relatively small in proportion to the resistance of the subject, then the tracheobronchial adenitis may be expected to precede the pulmonary lesion; and perhaps the latter may never reach the clinical threshold. And it is possible, too, that, as in two of the guinea pigs of group D, an earlier infection may produce a state in which a fresh infection of the pulmonary parenchyma leads to a local exudative process without much accompanying tracheobronchial adenitis.

Tubercle bacilli falling upon a mucous or respiratory surface are probably dealt with like minute foreign bodies, taken up by phagocytic cells and carried through the membrane into the underlying spaces. Some of the phagocytic cells will be taken up, with their bacillary contents, by fixed endothelial cells near the point of entry; others will pass along lymphatic channels to proximate or remote lymph nodes. Some may even pass through the lymph-node filters, and be swept on through the thoracic duct into the blood circulation to be arrested in the lungs, the spleen or elsewhere. Where the entering dose is very large and the resistance low, there will be heavy infection both locally, in the neighboring lymph nodes, and throughout the blood-filters of the body; and lesions may be expected almost simultaneously at all three zones of arrest. Where the entering dose is relatively small, most of the phagocyted bacilli will be arrested in the lymph nodes, and the few held up

locally at the point of entry will stand a good chance of being killed off in phagocytic cells. In the subsequent course of the infection, the relatively large deposits of bacilli in the nodes will play a part of supreme importance. Apart from cases of massive infection, in which generalization through the blood-stream is probably the rule, it is the "lesions of primary location," in a zone consisting of the portal of entry, the lymphatics draining it and the neighboring lymph nodes, that count in the subsequent fate of the patient; and their course and sequence is determined by the "infective potential" of the entering germs. The attempt to express these variants in the form of a "law" only leads to confusion. It is just as questionable to describe the pulmonary lesion as primary as it is to claim priority for the tracheobronchial adenitis. It is probable, however, that the lymph nodes provide for the tubercle bacilli of first infections the necessary site of unresisted multiplication which determines subsequent disease.

GENERAL SYMPTOMS FOLLOWING CONJUNCTIVAL INFECTION

Apart from the "lesions of primary localization" already discussed, the constitutional effects of tuberculous infection through the natural channel of the conjunctival membrane are worthy of brief consideration. Here, too, the "infective potential" seems to be the dominating factor. It is of great interest that all the animals of group A and all but two of group B, after having shown definite signs of infection following the original small preinfecting doses, had returned to what seemed normal health within six months of their first infection. This tendency to recovery does not seem to exist in guinea pigs infected by subcutaneous inoculation to the same extent.

In the case of group X, no lymph-node or ocular lesions could be found during the 175 days between the preinfecting and the reinfecting dose. This absence of clinical lesions I am unable to explain, but it is possible that the animals, being slightly older than those of groups A and B, were more resistant.

In group Y, as already stated, there were no observable lesions in any of the animals except one, after or during the eleven preinfecting doses. And yet the animals of this group were all deteriorated in health and, with two exceptions, died soon. In one of them, guinea pig 503, death occurred thirteen days after the reinfecting dose; so it could hardly have been due to the latter. There was a definite tuberculous lesion in the

right lung, clearly of fairly old standing, but peculiar in being surrounded by a zone of intense hyperaemia. There was no enlargement of the cervical or the tracheobronchial lymph nodes, nor were there any conclusive signs of generalized tuberculosis.

The same curious tendency to congestion around pulmonary tuberculous deposits was noted in guinea pig 502, which, however, had survived for three months after the reinfecting dose.

Two others, nos. 501 and 499, died without reinfection, and in neither could definite evidence of tuberculosis be found. It may be that their condition was related to that described by Krause and Willis (6) in guinea pigs subjected by them to repeated doses of tubercle bacilli.

As to the general symptoms following the larger reinfecting doses, it may be said that, while in all the animals examined postmortem there was generalization of the infection, the lesions of "blood distribution" seen in the viscera were less extensive than usually follows subcutaneous infection. The preimmunized animals tended to present lesions of a more chronic nature than those of the "controls."

CONCLUSIONS

1. Preinfection with living tubercle bacilli introduced through a "natural" portal of entry, the conjunctival mucous membrane, leads, under certain circumstances, to an enhanced resistance to subsequent infection with a lethal dose.

2. Preinfecting doses of very low infective potential appear insufficient to lead to a satisfactory degree of resistance; while preinfecting doses of very high infective potential tend to induce lesions so extensive as to be liable to activation by subsequent reinfection. There is evidence suggesting that, between these extremes, there is a zone of optimum dosage with an infective potential leading to considerably increased resistance, as indicated by a marked prolongation of the survival period after a lethal dose.

3. Preinfection with an attenuated strain appears more effective in the production of increased resistance than preinfection with a virulent strain.

4. In the tuberculosis induced by conjunctival instillation, the priority of lesion at the portal of entry and in the neighboring lymph nodes, respectively, depends chiefly upon the infective potential of the bacillary emulsion employed; eye lesions preceding, or being simultaneous with

lymph-node lesions when the infecting dose is large; lymph-node lesions showing priority to eye lesions when the infecting dose is moderate or small.

5. When conjunctival infection is induced by the instillation of successive small doses repeated at weekly intervals, the guinea pigs appear to fall into a state of general ill-health and tend to die early. In such animals, recognizable tuberculous lesions may be rare or absent. In a small group of animals infected by this method, the production of resistance to a subsequent lethal infection was not appreciable, either in enhanced survival-capacity or in a more chronic type of disease.

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SOME RELATIONS OF VITIATED AIR AND OF INADEQUATE FEEDING TO EXPERIMENTAL TUBERCULOSIS[1,2]

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with

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THE GENERAL PROBLEMS OF VENTILATION

The air of an occupied room may differ from the surrounding atmosphere in at least the following particulars: (1) diminution of oxygen, (2) increase of carbonic acid, (3) increase of temperature, (4) increase of humidity, and (5) the addition of organic matters through exhalations from the lungs and skin.

These conditions are all accentuated in proportion as the ventilation becomes inadequate, and life ceases under definite deterioration in the environment.

I cannot venture to impose upon you a recital of the fascinating chapter in Physiology and Hygiene which deals with the development of our knowledge in this field.

It is appropriate to recall that this city of Philadelphia has been the site of men and events which give it noble eminence in our story. Here lived, and here is buried, Benjamin Franklin, the Stagyrite of his age, who dealt with all things pertaining to human welfare. Here sojourned Brown-Sequard, whose brilliant imagination gave the basis for that physiological view of ventilation which it is the purpose of the present essay to exploit. Here the great bibliographer, John S. Billings, your venerated Weir Mitchell and the still present with us D. H. Bergey coöperated in 1895, in a masterly research on ventilation (1) which remains wholly modern in a library of investigations since founded on the subject. Leading physiologists everywhere shared in the reaction against the views of Brown-Sequard and D'Arsonval, who had claimed

[1] From the Research Department of the National Jewish Hospital, Denver, Colorado.

[2] Read at the forty-third annual meeting of the American Climatological and Clinical Association, Philadelphia, September 26, 1926.

that expired air contained a poisonous organic emanation, the removal of which was the chief object of ventilation. They agreed, in brief, that the positive results of Brown-Sequard were founded on faulty methods of experimentation; they failed to confirm the evidences for organic toxic excretions in the breath. The ingenuity of physiologists in this field has been directed chiefly toward finding a physical basis for the *uncomfortable sensations* through which we perceive the fouling of rebreathed air. They have demonstrated that when men are confined in a small closed space the sensory discomforts, which we attribute to poor ventilation, are quickly developed and soon become intolerable. During this period the air of the chamber will have become offensive to the normal smell, its temperature will have risen and its humidity increased. If at any period in the experiment the loss of heat from the body is facilitated by cooling the air, or increasing the evaporation of sweat by mechanical fans, sensory comfort is restored at once and the subjects seem unaware of any abnormal quality in the air, whatever its degree of pollution.

Many variations of this experiment have substantiated its results, though it is to be noted that the periods of observation were limited to minutes rather than hours, not to speak of days.

The monumental researches of the New York State Commission on Ventilation (2) attacked the problem of ventilation under experimental conditions far more closely resembling the ordinary relations of life than had hitherto been employed. Their work, begun in 1913 and fully published in 1923, embraced all obvious physiological and mental effects of varied conditions of ventilation, carried out on groups of people while at rest or working in a room in which the factors of ventilation,—air supply, temperature, humidity, etc.,—could be experimentally regulated.

We must accept the conclusion of the Commission summarizing their review of the history of experimental research into the rôle of organic pollution of respired air: "The weight of scientific evidence, as based on physiological investigation, was, however, overwhelmingly against the existence of such hypothetical substances."

I cannot venture to present, even in abstract, the elaborate researches of the Commission, but will limit my report to a few of their conclusions:

In most of the reactions studied in our experiments the influence of chemical vitiation of the atmosphere appeared to be absolutely *nil.* Temperature and humidity being the same, we compared fresh air containing 5 to 11 parts per

10,000 of carbon dioxide with vitiated air containing 23 to 66 parts and found no difference in body temperature, heart rate, blood pressure, Crampton index, rate of respiration, dead space of lungs, acidosis of the blood, respiratory quotient, rate of heat production, rate of digestion and protein metabolism.

Comfort of the subjects and their ability to do mental work were unaffected. But now listen to the positive results:

In regard to the performance of physical work, on the other hand, there appeared to be a distinctly harmful influence of the vitiated air. When the air was both warm and stale only 77 per cent as much physical work was performed as in cool fresh air. . . . . Finally, we found a marked influence exerted by stale air upon the appetite for food as determined by serving standard lunches to parallel groups of subjects, in stale and fresh air, respectively, but with the same temperature and humidity.

We may conclude then that the primary condition of good ventilation is the maintenance of a room temperature of 20°C. (68°F.) or below, without the production of chilling drafts; but that it is also important, *on account of certain subtle but real effects of vitiated air upon the appetite and inclination to work*,[3] to provide for an air change sufficient to avoid a heavy concentration of effluvia such as was associated in our experiments with a carbon dioxide content of 23 to 66 parts per 10,000.

If ever polemic were justified in scientific discussion this would seem to be an occasion. The proof that the morbid sensations induced by inadequate ventilation depend upon quantitative relations of the physical factors, temperature and humidity, is of fundamental importance. But the implied inference that this proof establishes the chemical innocuousness of breath-polluted air is utterly illogical; and we submit that such an inference inheres in most of the best work that has been done upon the subject. Thus, Hermans (3) is quoted as declaring that the problem of ventilation is sufficiently complex without founding its purpose on the accumulation of hypothetical foreign matters in the air. But the "subtle but real effects of vitiated air" stressed by the New York State Commission have escaped the attention of physiologists whose experiments have been limited to the duration, at most, ot a few hours, and apparently have been ignored in the designs for construction of many systems for artificial ventilation. In these days any suspicion of a

[3] Italics the authors'.

leaning toward teleology is fatal to the standing of a scientific advocate, but we assert that it is rational to surmise that the labile and drastic response of the heat-regulating mechanism of the body to an unfavorable environment, as usually found in vitiated air, may be Nature's admonition of more remote and insidious dangers from other (chemical) sources.

It is but a few years since we became convinced, through the respiration calorimeter, that human metabolism conforms to the principle of the conservation of energy. The metabolic functions of food seemed to have been essentially solved. But vitamines now broaden without demolishing our conception of nutrition.

The principles of neuromuscular and glandular physiology seemed fairly well established until the ubiquitous endocrines obtruded into our calculations.

Finally, we must emphasize the positive findings of the New York State Commission, wherein it appeared that repeated exposures of healthy men and women to air vitiated by exhalations to an extent denoted by accumulation of CO_2 to only 0.23 to 0.66 per cent were followed by distinct deterioration in two vital functions of first importance, namely, (1) appetite for food, which is the automatic regulator of the calorific intake and (2) the neuromuscular power, which is the motive agent of all human accomplishment.

THE SPECIFIC RELATIONS OF VENTILATION TO TUBERCULOSIS

I had long been ruminating upon these subjects when, more than five years ago, listening to the papers read at a meeting of this Society in Lenox, Massachusetts, an experimental method of attacking this problem of ventilation suggested itself.

Through *a priori* reasoning it seemed probable that, to successfully surmount the vicissitudes of evolution, normal animals and men have developed a high degree of immunity to deleterious agents arising from so common a misadventure as confinement in closed spaces. Indeed, to a student of Nature the thought must be adumbrated that such an accident may even involve physiological reactions protective against more serious ills; and for this interpretation I shall later venture to offer some shreds of experimental evidence.

But (reasoning further) when we consider the living being afflicted with tuberculosis, with its long period of latency through which a pathological metabolism summates every response to change of environment,

we are evidently introducing into the biological conception a modifying factor closely resembling the catalyst of the chemist.

I put it to you to visualize a school-room in which the young pupils are not robust but carry the restive germs of consumption. *That* is the major premise of any syllogism in the hygiene of ventilation.

It may now be clear what stimulus was the urge in these five years' work. It was the hope to define by experimental means the conditions of environment which lead to the transfer and development of tuberculosis. Several series of tedious and laborious investigations have been carried out, none of which would have been possible without the faithful coöperation of my younger associates in the task.

Some of these efforts have been already described in print and will be briefly dismissed.

The first problem attacked may be stated as follows (4):

Suppose we inoculate guinea pigs each with a minimal infective dose of virulent tubercle bacilli, six of these animals to be maintained in a comfortable and cleanly condition in as many large glass bell-jars, made airtight but communicating through rubber tubes. Activated by a filter pump an air-current is aspirated through the series of jars at any desired rate.

Thus, pure air was drawn into jar 1, was respired by guinea pig 1 and then passed to jar 2, and so on through the series. Guinea pig 1 breathed pure air, except as it was fouled by his own exhalations; in each jar the air became progressively more contaminated until in jar 6, the occupant was breathing the effluvia from six guinea pigs. The ventilation rate chosen was such that, neglecting certain rare mishaps, the carbon-dioxide content of the air in jar 6, remained between 1.5 and 2 per cent, while in jar 1 it was not over 0.1 per cent. We owe much to the kindness of Dr. Corper, Director of the Laboratory, who inoculated for us a large number of young male guinea pigs, each with one-millionth of a milligram of a highly virulent culture of tubercle bacilli.

Our experiment was continued for 220 days, during more than half of which time the animals were confined within the jars, which were large enough to accommodate food and a vessel of water. Unavoidable fouling of the jars necessitated their cleansing every 48 hours.

Many deaths occurred among the confined guinea pigs, each decedent being immediately replaced with an inoculated animal from the reserve group. It is understood, of course, that at the outset a large number of guinea pigs had been inoculated and set aside to serve as controls for those which we subjected to insufficient ventilation. When too late to correct the faults it was recognized that in three fundamental particulars the conditions

of our experiment were inimical to a true test of our hypothesis as to the detrimental influence of vitiated air. Thus, jar 1, whose occupant was ostensibly in a normal environment, was in close proximity to a steam radiator which could not be turned off. Throughout the winter months the temperature in jar 1 was frequently over 80°F. and was habitually two or three degrees higher than in jar 6. Moreover, through certain exigencies of service, the conditions in the animal room, in which the control guinea pigs were kept, became at that time most unsanitary, to a degree that the air was offensive. Again, it was found that the infective dose used by us for inoculation was not minimal but a thousand times too large; it should have been one-billionth of a milligram.

Nevertheless, in summarizing their results the authors were able to conclude:

> It may reasonably be maintained that guinea pigs inoculated with 0.000,001 mgm. of virulent tubercle bacilli, when confined for long periods in well-cleaned, communicating jars ventilated by an air-current which allows the accumulation of 1.5 to 2 per cent CO_2 of respiration in the last jar of the series, are subject to a higher mortality and somewhat more rapid and profound extension of disease than are control animals maintained in open cages. . . . . Finally, the evidence collected indicates that in rebreathed air the tuberculous process is somewhat prone to selective invasion of the lungs, with possibly complementary escape from infection of the abdominal organs.

It is to be suspected that if these experiments were repeated with correction of the technical errors which have been pointed out the results would furnish far more striking evidence of the toxicity of vitiated air.

POSSIBLE SENSITIZATION TO VITIATED AIR

On many occasions in the course of these and similar experiments the impression had been aroused that guinea pigs, when reëxposed to breath-polluted air, behaved differently as compared with normal animals exposed for the first time. This result suggested that the vitiated air might, under certain conditions, sensitize the respiratory apparatus, which itself would be crucial evidence of a foreign-protein content in the medium. It may be recalled that there is a considerable group of well people who frequently suffer pathological reactions when confined in crowded assemblies. The dependence of asthma and hay fever on various known antigens is of common knowledge.

By the use of our jar ventilation apparatus, 103 guinea pigs were subjected to courses of "sensitizing" exposures to highly vitiated air, and later, after the lapse of several weeks, were reëxposed, in the presence of normal animals as controls, to the same conditions. In 53 of our tested

animals there seemed to be positive though slight signs of anaphylactic reaction on reëxposure to vitiated air. In 50 no definite conclusions could be drawn. Here again we find a preponderance of evidence in favor of organic air pollution, but no positive proof. These experiments have been recorded in detail elsewhere (5).

During several months after completion of the foregoing research numerous deaths from so called "spontaneous" tuberculosis occurred among the guinea pigs which had been used in our experiments and were afterward stored in a room which had long harbored tuberculous animals. This extraordinary epidemic has been analyzed in another place (6). Major Falisi, Pathologist to the U. S. Fitzsimons General Hospital, Denver, has kindly given us the details of an unpublished and still more decimating scourge of accidental tuberculosis, which occurred among his own guinea pigs about the same time as ours.

It seemed plausible that some environmental condition had operated upon our guinea pigs in such a way as to lower their physiological resistance toward the implantation and development of tuberculous infection. A prolonged investigation was accordingly undertaken to determine, if possible, the nature of the influence which would lower resistance of the guinea pig toward tuberculosis. Our first problem was to determine whether repeated exposures of guinea pigs to highly vitiated air, under conditions that have been detailed, alter the rate and extent of propagation of tuberculosis implanted in guinea pigs by experimental inoculation.

Doctor Corper again kindly prepared for us a suspension of highly virulent tubercle bacilli, of which each cubic centimetre was estimated to contain one-billionth of a milligram of bacilli. As set forth in another place (6), the injected dose of one cubic centimetre probably contained an average of about six bacilli. Doctor Corper inoculated for us 100 young male guinea pigs, weighing 200 to 300 gm. each. The injections were made under the skin of the left flank after plucking the hair.

The refinement of technique was later demonstrated by the plain, macroscopic development of tuberculosis in every animal except one that died within five days.

Half of our inoculated animals were retained as controls while half were subjected to vitiated air. They were distributed equally in the same cages under completely sanitary conditions.

The experiment was conducted in two phases, according as the inoculation with tubercle bacilli preceded or followed the exposures to vitiated

air; and the guinea pigs devoted to each phase were distinguished as follows:

Lot 1: Fifty guinea pigs were inoculated each with 0.000,000,001 mgm. tubercle bacilli, August 23, 1923, approximately 32 days *before* beginning exposures to vitiated air. Divided into Lot 1a and Lot 1b; Lot 1a, 25 "jar" guinea pigs. Guinea pigs 1 to 12 were exposed to vitiated air twice with a two-day interval, and guinea pigs 13 to 25 to vitiated air twice with a one-day interval. Lot 1b, 25 controls, were set aside for observation.

Lot 2: Fifty guinea pigs were inoculated each with 0.000,000,001 mgm. tubercle bacilli on October 29, 1923, approximately 22 days *after completion* of exposures to vitiated air. Lot 2a, 25 "jar" guinea pigs. Guinea pigs 1 to 12 received *three* exposures to vitiated air on alternate days, and guinea pigs 13 to 25 received *two* exposures on alternate days. Lot 2b, 25 controls, were set aside for observation.

Of the 50 guinea pigs appropriated to each phase of our experiment 25 were treated with vitiated rebreathed air and 25 were set aside for controls. The exposures to polluted air were made in the communicating jars already described. Each of the first three jars contained a full-grown guinea pig, whose sole function was to increase contamination of the air-current reaching jars 4 to 6. Our experimental group of 25 young guinea pigs was divided into four lots of 6 each, two of the number being allotted to each of the jars 4 to 6, the odd guinea pig being added to jar 4. In successive exposures each animal was, of course, returned to its proper jar. Each group of 6 guinea pigs received two separate exposures to vitiated air and on alternate days. The ventilating current through the jars was so regulated that the vitiation of the air gradually increased to a degree productive of more or less marked dyspnoea, where it was maintained for an hour or two, when the guinea pigs in jars 4 to 6 would usually be in great distress; at this time the CO_2 content in jar 4 would approximate 7 to 12 per cent, and 12 to 14 per cent in jar 6. There was no evidence that this drastic treatment produced any pathological after-effects.

It will be observed that the exposures of the guinea pigs in Lot 1a were begun about 32 days *after* inoculation, and therefore during the active progress of their tuberculosis but probably long before the macroscopic deposition of tubercles in the lungs.

On the other hand, the exposures to vitiated air in Lot 2a were completed about 22 days *before* their inoculation. During this period op-

TABLE 1

Lot 1: Fifty male guinea pigs, each inoculated with 0.000,000,001 mgm. tubercle bacilli, July 23, 1923

LOT 1A: 25 GUINEA PIGS EXPOSED TWICE TO VITIATED AIR 32 DAYS *after* INOCULATION				LOT 1B: 25 CONTROLS NOT EXPOSED TO VITIATED AIR			
All animals survived more than 50 days				Observations limited to 22 animals which survived more than 50 days			
Fate of guinea pigs	Days lived after inoculation, average	Average number of units of infection		Fate of guinea pigs	Days lived after inoculation, average	Average number of units of infection	
		Lungs	Abdomen			Lungs	Abdomen
10 guinea pigs died	81	2.0	2.8	11 guinea pigs died	84.9	1.64	2.64
15 guinea pigs gassed	112.1	2.33	2.2	11 guinea pigs gassed	112.6	1.73	1.82
Average total.....	96.55	2.17	2.5	Average total.....	98.8	1.69	2.23

Summary: Lot 1a shows 54.3 per cent of total infective units of *a* and *b*, thus:

Lungs: 56.2 per cent
Died 54.9 per cent
Gassed 57.3 per cent
Abdomen: 52.8 per cent
Died 51.0 per cent
Gassed 54.7 per cent

TABLE 2

Lot 2: Fifty male guinea pigs each inoculated with 0.000,000,001 mgm. tubercle bacilli, October 29, 1923

LOT 2A: 25 GUINEA PIGS EXPOSED TO VITIATED AIR 22 DAYS *before* INOCULATION GUINEA PIGS 1 TO 12 THREE TIMES GUINEA PIGS 13 TO 25 TWO TIMES				LOT 2B: CONTROLS, 25 GUINEA PIGS NOT EXPOSED TO VITIATED AIR			
Study of 22 guinea pigs surviving upward of 55 days				Study of 22 guinea pigs surviving upward of 55 days			
Fate of guinea pigs	Days lived after inoculation, average	Average number of units of infection		Fate of guinea pigs	Days lived after inoculation, average	Average number of units of infection	
		Lungs	Abdomen			Lungs	Abdomen
14 guinea pigs died	84.6	1.4	2.4	14 guinea pigs died	84.8	1.6	2.9
8 guinea pigs gassed	129.3	2.5	2.9	8 guinea pigs gassed	129.5	2.4	3.0
Average total.....	106.9	1.95	2.65	Average total.....	107.2	2.0	2.95

Summary: Lot 2a shows 48.2 per cent of total infective units of *a* and *b*, thus:

Lungs: 49.3 per cent
Died 46.5 per cent
Gassed 51.0 per cent
Abdomen: 47.3 per cent
Died 45.2 per cent
Gassed 49.2 per cent

portunity was given for the development of any hypothetical sensitization of the respiratory apparatus and also allow time for recovery from possible traumatic effects from the exposures.

The crux of our experiment consisted, obviously, in an exact comparison of the intensity and distribution of tuberculosis, as determined by autopsy, in the animals which had been exposed to vitiated air and in those (controls) which had not been so exposed. In the autopsies the various lymph nodes and organs of each subject were studied seriatim, and the magnitude of their tuberculous involvement was estimated. We adopted an arbitrary scale of four units in which + represented the slightest degree of tuberculous disease and ++++ the maximal in-

TABLE 3

Lot 2a: Distribution of infection and number of exposures to vitiated air

A: LOT 2A, JAR GUINEA PIGS, 1 TO 12: 1 DIED: RECEIVED 3 EXPOSURES TO VITIATED AIR				*B:* LOT 2A, JAR GUINEA PIGS, 13 TO 25: 2 DIED: RECEIVED 2 EXPOSURES TO VITIATED AIR			
A	Days lived after inoculation, average	Average number of units of infection		*B*	Days lived after inoculation, average	Average number of units of infection	
		Lungs	Abdomen			Lungs	Abdomen
8 guinea pigs died	85.2	1.66	2.5	6 guinea pigs died	84.0	1.1	2.1
3 guinea pigs gassed	129.0	3.0	3.0	5 guinea pigs gassed	129.6	2.2	2.8
Average total.....	107.1	2.33	2.75	Average total.....	106.8	1.65	2.45

In *A* the average total infective units formed 55.3 per cent of the total of *A* and *B*.

In *A* the average of *pulmonary* infective units formed 58.5 per cent of the total pulmonary units of disease.

volvement. It was specifically our design to contrast the extent of disease in the lungs and abdominal organs, respectively. The results of our experiments are condensed in tables 1 and 2.

It will be observed that no account was taken of animals dying from intercurrent affections within 50 to 55 days after inoculation. In Lot 1 the period of observation was continued 116 days, when the guinea pigs remaining alive were killed by illuminating gas as rapidly as was consistent with their thorough examination, which required 3 days. Two of the animals of Lot 1a and one of Lot 1b had been killed well before the close of the period of observation.

Discussion of Tables 1 and 2: Lot 1a was made up of animals which

received their exposures to vitiated air about 32 days after their inoculation with tubercle bacilli. That the drastic respiratory treatment did not specifically affect their well-being is shown by the fact that none of them died within 50 days of inoculation or within 19 days of their last exposure in jars. Of the control group, Lot 1b, 3 guinea pigs had died 5, 34 and 41 days after inoculation; the two latter showed slight abdominal tuberculosis.

Of the 50 guinea pigs in Lot 1, the experimental group, Lot 1a, shows 54.3 per cent of the total infective units of tuberculosis of groups a and b. But Lot 1a shows 56.2 per cent of the total *pulmonary* infection, and this proportion rises to 57.3 per cent in the guinea pigs which were gassed more than 112 days after inoculation. The relative extent of abdominal disease in the jar guinea pigs, as contrasted with the controls, was notably less.

Apparently, then, some influence, be it mechanical or chemical, has favored the deposition of tubercle in the lungs of animals which were subjected to vitiated air in our jar experiments during the course of active tuberculosis.

Krause (7), with his associates, especially Willis (8), has performed the useful service of tracing the distribution and activities of tubercle bacilli from the moment of their inoculation. It is regularly found, after subcutaneous injection of tubercle bacilli in the inguinal region, that, as tested macroscopically, tuberculosis first invades, more or less seriatim, the abdominal lymph nodes, then the spleen and liver and, far later, the lungs. We have found enlargement and degeneration of the tracheobronchial lymph nodes considerably antedating the presence of macroscopic tubercle in the lungs.

With the very small infective dose used by us, guinea pigs between 30 and 40 days after inoculation show distinct enlargement and more or less degeneration of the abdominal lymph nodes and spots suspiciously like tubercles in the normally appearing spleen and (or) liver.

In this series of experiments we have not found macroscopic tubercles in the lungs under 58 days after inoculation, and this latent period is usually considerably longer.

When we consider table 2, in which are represented the data from Lot 2, of which the 25 experimental animals were exposed to rebreathed air about 22 days *before* their inoculation, the results on superficial examination might be interpreted to support conclusions directly opposite to those drawn from table 1. For we find that our experimental jar guinea pigs showed but 48.2 per cent of the total infective units. *It would appear that the preliminary exposures to the drastic experiences of the jar experiments had actually increased the resistance against the spread of disease caused by the subsequent inoculation.* This is an interpretation that can be neither affirmed nor denied, and it will be referred

to later. The greater absolute amount of disease found in the gassed guinea pigs of Lot 2, as compared with the similar group of Lot 1, is obviously to be explained by the longer time allowed the former for the development of their disease.

Even so, we find that, comparing Lot 2a with their controls, Lot 2b, the relative extent of *pulmonary* disease increases from less than 46.5 per cent in guinea pigs dying after an average of 84 days to over 51 per cent in guinea pigs gassed after 129 days. That is to say, there was a decided progressive relative preponderance of pulmonary infection in the experimental jar guinea pigs.

Evidence of specific pulmonary susceptibility in the animals which had breathed polluted air is strengthened by other considerations. It may be remembered, namely, that the first 12 guinea pigs of Lot 2a were exposed, in groups of six, to vitiated air in our jars on *three* occasions, the last exposure occurring 21 days before their inoculation. The 13 remaining guinea pigs of Lot 2a received only *two* similar jar exposures, the last occurring 17 days before inoculation; the first group had, therefore, four more days than the second to recover from any hypothetical injury due to the vitiated air before their inoculation. In table 3 the 25 guinea pigs of Lot 2a are considered in two groups. In the first, *A*, the autopsy reports are based on 12 guinea pigs that had received *three* separate exposures to vitiated air; in the second group, *B*, the 13 guinea pigs had been subjected to but two exposures. In group *A* the average total infective units formed over 55.3 per cent of the total for *A* and *B*, and the average of pulmonary infection formed 58.5 per cent of the total pulmonary units of disease. That is to say, comparing the quantity and distribution of tuberculosis in two groups of guinea pigs, one of which had received *three* and the other but *two* exposures to vitiated air preceding their inoculation, it was found that the former group presented the greater proportion of the total tuberculosis units and a still greater proportion of the pulmonary infection.

Our general discussion has been founded on the hypothesis that exposure to intensely vitiated air lowers, in guinea pigs, the normal resistance to the spread of experimental tuberculosis, and especially as regards the lungs.

In a publication (5) already quoted evidence is presented which indicates that guinea pigs may be sensitized to the concentrated emanations of their fellows. The possibility has been suggested above (p. 338) that the result of such a "sensitizing" exposure (as in Lot 2a, p. 335) is

to actually endow the pulmonary apparatus with an increase of its natural resistance against pulmonary infection, which should be evidenced by abnormally late development of pulmonary disease. It is quite credible that such artificial resistance, once overcome, would result even in acceleration of the infectious process.

In this connection we venture to cull from our notes certain suggestive data. It may be remembered that the members of Lot 1a were exposed to vitiated air *after* their infective injection, while those of Lot 2a were exposed to it *before* inoculation. Five guinea pigs of Lot 1a died 51 to 73 days after their inoculation (average 63.6 days). Each of them showed *one unit* of pulmonary tuberculosis, with somewhat greater abdominal involvement. Five guinea pigs of Lot 2a died 58 to 75 days after their inoculation (average 61.8 days).

Each of them showed *one unit* of abdominal tuberculosis but *none* showed tuberculosis of the lungs. Manifestly, these data suggest that preliminary exposures to vitiated air act upon the lungs in a way to defer tuberculization from subsequent inoculation, and the establishment of the hypothesis suggested needs only multiplication of similar experience.

The results of our experiments point toward the following conclusions.

1: Brief exposures of tuberculous guinea pigs to air highly vitiated by inadequate ventilation specifically favors deposition of tubercles in the lungs. No evidence is offered as to whether these results are due to chemical (immunological) or to mechanical changes in the lungs.

2: When normal guinea pigs are exposed to similarly vitiated air and are later inoculated with tubercle bacilli, they likewise exhibit, as compared with controls, a relatively increased development of tubercles in the lungs, apparently preceded by a period of temporarily increased resistance.

THE RELATION OF PREVIOUS EXPOSURES TO VITIATED AIR TO THE DEVELOPMENT OF CONTACT TUBERCULOSIS

By obvious reasoning we were led to seek for evidence that normal guinea pigs which had been repeatedly exposed to highly vitiated air would show, as compared with others not so exposed, increased incidence of "spontaneous" disease when confined together with animals artificially inoculated with tuberculosis.

Our experiment employed 100 guinea pigs having an average weight of 250 gm. At that time a dearth of material necessitated the use of a

certain proportion of female animals which were, of course, kept segregated. Our animals were maintained in a large loft, sufficiently lighted, which had not been used for similar purposes. The guinea pigs were confined in metal cages built side by side, four in a series, with partitions of coarse-meshed wire, making a total of four tiers of four cages each. The cages had a uniform floor space of 21 x 23 inches, and a height 11 inches. At the outset of the experiment each cage contained a total of 7 guinea pigs. With exceptions to be noted, 3 of the animals in each cage had been exposed to vitiated air, 3 were normal controls and one had been inoculated with tubercle bacilli subcutaneously in the groin; the latter animal was conveniently known as the *t* guinea pig. This individual usually developed an ulcer at the site of inoculation, and when

TABLE 4

Effect of vitiated air on incidence of contact tuberculosis

GUINEA PIGS	LOT 1		LOT 2		LOT 3		LOT 4	
	Jar	Control	Jar	Control	Jar	Control	Jar	Control
Number	12	14	12	13	12	12	12	12
Died	5	3	3	6	3	7	7	5
Number tuberculous	0	1	0	1	0	1	2	1
After days' exposure noted in lines four and five		96		177		250	129* 334	232*
Total days of observation	317		321		340		384	

* Guinea pigs occupied the same cage.

one died it was replaced from a store of inoculated subjects. The exposures to vitiated air occurred in the series of 6 jars already noted, two guinea pigs being allotted to each jar.

The contamination of the ventilating air-current increased progressively from jar 1 to jar 6. Our treatment was especially drastic, for, at the end of an exposure of an hour or more, the CO_2 content of jar 1 would approximate 4 or 5 per cent, and of jar 6 would be 13 to 15 per cent. Our guinea pigs were divided into four equal groups corresponding to the four tiers of cages, and were recorded as Lot 1, Lot 2, etc. The "jar" guinea pigs of each group were exposed to vitiated air on 3 to 6 successive days and then, after a resting period of 10 to 14 days, received a final exposure. The results of the experiment are summarized in table 4.

The members of Lots 1 and 2 were survivors of an epidemic that had affected several individuals, though all seemed in excellent condition when the experiment was begun. All of Lot 2 and one-quarter of Lot 1 were females. A tuberculous (*t*) guinea pig was added only to the two terminal cages of each tier of four cages; therefore, the occupants of the end cages were in direct, and those of the intervening two cages of each tier in indirect contact with a tuberculous animal. The food consisted of rolled oats, dry bread and water, with the addition of cabbage or carrots to supply vitamines. The cages were scraped clean two to four times weekly.

The essential data for each lot are separately set down in table 4. One of the controls of Lot 2, which died early, was excluded. Considering Lot 1, it is seen that during 317 days' observation one guinea pig died with tuberculosis; this was a *control* guinea pig which had been exposed to infection for 96 days. It should be noted that the probable direct cause of death in this animal was an acute pleuropulmonary infection; there was a relatively minor degree of tuberculous involvement.

The details for Lot 2 should be clear. Here likewise only one, a control guinea pig, died of generalized tuberculosis, and that after an exposure of 177 days. It should be noted that this animal had been affected in the epidemic antedating the experiment, but had apparently completely recovered.

It is important to note that each of these deaths from tuberculosis occurred in a terminal cage harboring an experimentally tuberculous animal.

In Lots 1 and 2, of 24 guinea pigs directly exposed to tuberculosis, two, or 8.3 per cent, contracted the disease, and both of these were controls. In a continuation of this experiment, to be described later, the dependence of contagion upon intimacy of contact will be further illustrated.

The jar guinea pigs of Lots 1 and 2 had received four separate exposures to vitiated air within about two weeks preceding their contact with tuberculosis.

The experiments upon Lots 3 and 4 differed in material details from the foregoing. All of the animals were young male subjects, with a clear history as to disease. Each of the eight cages harboring the guinea pigs contained 7 animals, of which 3 had been exposed to vitiated air, 3 were normal controls and one was actively tuberculous, having been previously inoculated. Of Lot 3 the jar guinea pigs received six separate exposures to vitiated air during the first 3 weeks after the ex-

periment was started. Of Lot 4 the jar guinea pigs were exposed seven times to vitiated air within the first two weeks of the experiment.

In Lot 3 one guinea pig, and that a *control*, died of generalized tuberculosis after an exposure to infection of 250 days. In Lot 4 we find for the first time manifestations of tuberculosis among the "jar" guinea pigs, two of which are represented as having the disease. One died of generalized (macroscopic) tuberculosis after a contact exposure of 334 days; but the cause of death in the other was an acute pleuropericardial inflammation, with macroscopic evidences of tuberculosis. It should be remembered that of Lot 4 the jar guinea pigs had suffered seven drastic exposures to vitiated air.

It is notable that in each of these cases from Lot 4 smear preparations from various suspected organs disclosed, respectively, but a single acid-fast bacillus. In Lot 4 one control guinea pig died of generalized tuberculosis after 232 days. This animal had developed xerophthalmia during the course of the experiment.

We conclude from this section of our work that the danger of transfer of tuberculosis from a diseased to a healthy animal is probably strictly proportional to the intimacy of contact (nothing new). But our provisional hypothesis, which proposed to account for our epidemic of "spontaneous" tuberculosis by a lowering of pulmonary resistance through previous exposures to highly vitiated air, has found no support whatever. We will not now dwell upon the contrary interpretation of our results, for the number of experiments is wholly inadequate to serve as a basis for argument.

IS THERE A RELATION BETWEEN FOOD VITAMINES AND TUBERCULOUS CONTAGION?

Our research just described had been essentially barren in positive results, and we were led to look further for environmental factors which might depress vital "resistance" and accordingly facilitate the propagation of ingested tubercle bacilli.

It happened that during the time when our data on "spontaneous" tuberculosis were being collected the guinea pigs in our breeding-house, maintained in excellent sanitary condition, suffered from a decimating mortality. It was found too late that the symptoms of the disorder were such as characterize reaction to deficiency of vitamines in the diet, especially as pertaining to the antineuritic factor. We are especially in-

debted to Dr. G. W. Stiles, of the U. S. Bureau of Animal Industry, for insisting on this point of view. Investigation developed the fact that the main or only supply of green food enjoyed by the guinea pigs during the "epidemic" had been a rather poor quality of alfalfa. Glenny and Allen (9) describe such an epidemic among their own guinea pigs due to dietary deficiency which evidently predisposed to various bacterial infections.

An extensive search of the literature failed to reveal any work which attacked the identical problem we had in mind. There is found, however, everywhere evidence for a causal relation between vitamine deficiency and lowered physiological tone, with the suggestive deduction that resistance to pathological invasion is a corollary thereto. The general tenor of work already published may be gathered from the following extracts from the literature:

C. H. Werkman (10) found that "rats, rabbits and pigeons suffering from pronounced vitamine deficiencies suffered a marked break in their resistance to infection." The vitamines considered were *A* and *B*, and the infective agents the germs of anthrax and pneumonia.

As to the guinea pig it was found that lack of vitamine C produced a slight but definite break in their resistance to infection by the pneumococcus and anthrax bacillus. It is held that the reduced body temperature caused by vitamine starvation is concerned in the reduced resistance to infection. Guinea pigs lacking vitamine C do not differ from normal animals in their ability to produce specific agglutinins for the typhoid bacillus, nor is there revealed any injury to the phagocytic mechanism. Rats on low vitamine diet are more susceptible to diphtheria toxin, but their ability to produce antitoxin is not impaired (11). Leichtentritt (12) inoculated a number of guinea pigs with tubercle bacilli; to the normal diet of some of these he added a daily portion (10 to 25 cc.) of neutralized lemon juice, containing vitamines B and C; the control animals succumbed to disease much earlier than the treated ones. He found, on the contrary, that codliver oil, rich in vitamine A, in large amounts was wholly lacking in beneficial influence.

Findlay (13) remarks that the experience of all observers has gone to show that animals fed on diets deficient in vitamines are far more susceptible to bacterial infection than those fed on complete diets. He then gives evidence that guinea pigs with scurvy, though showing few clinical symptoms, are less resistant to bacterial infection than are normal controls. He also points out that "the reduction of natural immunity is related to the fall in body temperature produced by the B-deficient diets."

Abderhalden (14) demonstrated that tissue respiration is greatly lowered through deficiency of vitamines in the diet. Zilva (15) found that in guinea pigs wide variations in the diet had no effect on the production of agglutinins, complement and amboceptor.

In a careful piece of work Maurice I. Smith (16) found that in guinea pigs experimentally infected with tuberculosis the administration of codliver oil was not definitely beneficial, either as regards the weight curve, the length of life, or the extent of the disease process.

Lange and Simmonds (17) studied in tuberculous rats the influence of diets varying widely in protein content. They could find no significant difference in the reaction to infection either in the general condition and weight-curves or in the gross and microscopic autopsy findings. They found more positive results from a diet deficient in salts but otherwise adequate.

Prausnitz and Schilf (18) found insufficient diet to have a baleful influence on the course of experimental tuberculosis. They fed guinea pigs on a scorbutic diet and then infected them with tuberculosis, along with normal controls. The scorbutic tuberculous animals gave a less well-marked tuberculin skin reaction and less febrile reaction (in these the temperature dropped) than the nonscorbutic tuberculous animals.

E. Coland (19) tested in tuberculous guinea pigs the lack of dietary *C*. He found that in such animals the adenopathy and the extension of lesions to the spleen were hastened in comparison with the controls.

Bieling (20) found that tuberculous guinea pigs were far more sensitive to the deleterious influence of a diet deficient in vitamine C than were the normal controls.

Such monographs as those of McCollum (21) and of Sherman (22) are replete with information bearing on these conceptions.

It is not, then, strange that there arose in us a suspicion that the origin of "spontaneous" tuberculosis among our own guinea pigs might be explained by a depreciation of their vital resistance, due to inadequate feeding associated with an environment known to have been contaminated by tuberculosis.

Our own work has incidentally substantiated the deduction to be drawn from the literature, namely, that guinea pigs known to be tuberculous succumb more quickly to their disease in proportion to the limitation of vitamines in their food.

But our problem was to determine whether the deprivation of vitamines lowered the bars of that "resistance" which in every normal animal opposes the development within its body of pathogenic microörganisms. Is the guinea pig whose diet is deficient in vitamines more susceptible to tuberculous contagion, when closely associated with a tuberculous companion, than a guinea pig on a full diet maintained under the same conditions?

There is a real distinction between the *contracting* of tuberculous infection and the *development* of tuberculous disease.

In the former case we may postulate the entrance of ingested tubercle bacilli into lymph nodes with only sufficient reaction to excite the formation of a resting tubercle. In the latter case metabolism of the bacilli becomes active and continuous and the examiner recognizes "clinical tuberculosis."

The guinea pig is characterized by the narrowness, if not indeed, the absence of the zone of latent tuberculosis. In our experience one-billionth of a milligram of a virulent culture, containing approximately six tubercle bacilli, proved constantly infective.

Yet we must suppose that in the experiments about to be described the guinea pigs that were exposed to, but did not contract tuberculosis, must nevertheless have ingested and destroyed tubercle bacilli. It seems to us, contrary to general opinion, that the guinea pig is preëminently

adapted for use in such an experimental investigation as that to be described.

Our problem was to maintain normal guinea pigs in close association with companions which had been experimentally inoculated with tuberculosis and to reduce the vitamine content in the diet to as low a measure as was consistent with life. It was assumed that the incidence of tuberculous infection developed in the experimental animals, as compared with well-fed controls, would furnish evidence as to the rôle of vitamines in affecting the threshhold of resistance against contact tuberculosis.

Our basic diet consisted of an abundant supply of rolled oats, dry rye bread, part of the time a little timothy hay, and water; such a diet is recognized as deficient in the vitamines necessary to normal nutrition.

We assumed that green cabbage added to the above ration would fulfil all ordinary requirements for nutrition; its vitamine content has been listed as "good" for vitamines A and B and "rich" for C. We are indebted to Professor E. V. McCollum for the hint that the minimum amount of cabbage which would suffice to supply the daily needs of a guinea pig is about 10 gm.

Our experiments were performed upon 97 healthy male guinea pigs, weighing from 200 to 400 gm. each. They were studied in four groups distributed among 16 clean metal cages, such as have been previously described. To each cage were allotted 6 guinea pigs, in one cage 7, and to each cage also was added a single guinea pig which had been inoculated subcutaneously several weeks before with 0.1 to 0.2 mgm. of a virulent culture of tubercle bacilli. As a rule the tuberculous guinea pigs developed an open ulcer at the site of inoculation. As each inoculated guinea pig died it was replaced by another which had been prepared in a similar way. The high mortality supervening among the inoculated guinea pigs under restricted cabbage ration led, late in the experiments, to separate feeding of the inoculated guinea pigs for some minutes each day.

The cages were scraped clean, first thrice, then twice and later once weekly. After observation of a week or two under full diet, each group of guinea pigs was continued on the basic vitamine-poor diet, but the amount of cabbage allotted to each cage was reduced to a quantity equivalent to about 10 gm. for each guinea pig daily. Whenever the animals continued to thrive well for two or three weeks the administration of cabbage was reduced to 4, 3, 2 or even one feeding a week.

The determinants for regulation of the cabbage dietary were the appearance of the guinea pigs, as to the roughness of coat, weight or, especially, the mortality rate. The latter factor repeatedly made it necessary to return for a period to the 10-gm. daily ration of cabbage per guinea pig. Weighings were made regularly once a month.

Careful postmortem examinations were made upon all guinea pigs. When those that had not been experimentally inoculated showed lesions suggestive of tuberculosis, smear preparations were made therefrom and examined for tubercle bacilli. When these were negative, emulsions were usually made from the suspected organs and injected into normal guinea pigs. No animals were recorded as having contracted tuberculosis without previous demonstration of tubercle bacilli in their tissues.

TABLE 5

Vitamine deficiency and tuberculosis

PERIODS OF EXPOSURE TO INFECTION	NUMBER OF DEATHS, ALL CAUSES	DIED WITH TUBERCULOSIS	
		Number of guinea pigs	Days exposed
days			
1–120	17	0	
121–240	23	1	179
241–360	36	2	241*, 273*
361–480	21	2	311, 343

* Guinea pigs occupied the same cage.

It had been found in previous observations (table 4) that normal guinea pigs might develop tuberculosis when confined in the same cage with a tuberculous animal, and the deaths occurred under such conditions after exposures as short as 96 and 129 days.

The lethal effect of deprivation of vitamines in the diet was evidenced by the high mortality,—usually with signs of pneumonia but often without discernible lesions,—in our experimental animals.

That the exposures to contact-tuberculosis among our groups of guinea pigs subjected to a diet deficient in vitamines were sufficiently long to give fair opportunity for the transfer of contagion is evidenced by the fact that the deaths of our 97 experimental animals were distributed in time as shown in table 5.

It will be seen in the table that 17 pigs died within the first four months of exposure to tuberculosis; 23 pigs died within the second four months,

and so on. Thus, there is no doubt that at least 80 of our experimental animals were under periods of combined vitamine deficiency and exposure to tuberculosis to give, on the basis of known facts, sufficient opportunity for the acquirement and development of tuberculosis. Yet we find that out of 97 animals only 5, or 5.15 per cent, could be proved to have contracted the disease. Two of these, the guinea pigs dying after exposures of 241 and 311 days, respectively, had been harbored in the same cage. It must be admitted, however, that in several instances postmortem gross appearances led to the suspicion of tuberculous infection, which we ourselves could not verify as such. We are greatly indebted to Dr. H. E. Robertson and Dr. J. W. Kernahan of the Mayo Clinic, who had the suspected tissues sectioned and stained for tubercle bacilli, but with negative results.

We perhaps committed a technical error in using for our controls for our vitamine-deficient animals the apparently healthy guinea pigs of greater age which were left over from our preceding experiment (table 4). Most of these controls had already been exposed for more than 300 days to contact with guinea pigs having active tuberculosis. A consideration of all the data offered shows our procedure to have been quite defensible.

Our control group contained but 60 guinea pigs, about one-quarter of which were females, properly segregated. The control animals were much less crowded than the experimental group; they were associated in each cage with a tuberculous animal. They received, in addition to the basic diet, abundance of cabbage besides, in its season, green grass. It is worth remarking that the males, never the females, among the controls developed in some cases extensive ulcerations in the skin of the back. When a guinea pig with such a lesion was isolated the ulcer would rapidly heal. The ulceration was obviously initiated and extended by combat wounds inflicted by natural bullies among the guinea pigs. Such lesions were never observed in the pigs on a diet deficient in vitamines

The last of our experimental guinea pigs, those on a low-vitamine diet, had died 462 days after beginning the experiment. There still remained, of the 60 controls, 32 members in apparently good condition. These were killed by illuminating gas, and were found to be free from tuberculous infection.

The history of the control group during the period of our "vitamine" experiment is summarized in table 6. It is here found that 6 of the

control group had contracted tuberculosis. This represents a mortality of 10 per cent, nearly twice as great as that of the low-vitamine group of table 5.

But it should be noted that three of the tuberculous animals, those of Lot 1, were confined in the same cage; they were doubtless subjected to excessive intensity of infection. At least in one case, the guinea pig of Lot 4 recorded as dying of tuberculosis after an exposure of 62 days, the infection was probably contracted in the previous experiment, summarized in table 4.

TABLE 6

Full diet and tuberculosis (continues table 4)

GUINEA PIGS	LOT 1		LOT 2		LOT 3		LOT 4	
	Jar	Controls	Jar	Controls	Jar	Controls	Jar	Controls
Number	7	11	9	7	9	5	5	7
Died	2	5	3	5	2	3	3	5
Gassed	5	6	6	2	7	2	2	2
Number tuberculous	1	2	0	1	1	0	1	0
After days' exposure noted in lines five to eight	245* [562]	123* [440] 446* [763]		191	218 [558]		62 [446]	
Total days of observation	462 [779]		449 [770]		414 [754]		364 [748]	

* Three guinea pigs in the same cage. The numbers in brackets represent the sums of periods in tables 4 and 6.

Table 6 is a direct continuation of table 4, and retains the nomenclature of the latter except that the "gassed" guinea pigs are enumerated, and in the last line there are added in brackets the periods of total exposure to infection as represented in the two tables.

Our experiments illustrate well the parallel between the intensity of infection in an environment and the transfer of tuberculosis by contact. Thus, the 99 normal guinea pigs recorded in tables 4 and 6 had been distributed equally among 16 cages, in each of which was finally maintained also a guinea pig inoculated with tuberculosis. In the course of about two years 12 of the normal guinea pigs died with tuberculosis. Six of these deaths occurred in two cages, three in each cage.

The 97 normal guinea pigs used in the vitamine-deficiency experiment

were also distributed between 16 cages. Five of the animals died with tuberculosis, two of them in a single cage.

In spite of a full vitamine diet 6 or 8 of the control group within the two years developed signs of vitamine deficiency, such as keratitis, cries of distress on handling, or wry neck. Only one guinea pig presenting such symptoms died of tuberculosis.

CONCLUSIONS

So far as our limited number of observations may serve as a basis for deduction we must conclude:

1. That in normal guinea pigs the acquirement of tuberculosis by contagion depends upon two factors, namely, the duration and the intensity of exposure.

2. We have referred to the evidence for a degree of sensitization as induced by breathing highly vitiated air.

3. It appears that when guinea pigs are exposed to highly vitiated air early in the course of induced tuberculosis there is a preponderant deposition of tubercle in the lungs as contrasted with other organs.

There is significant evidence for the conclusion, contrary to our original hypothesis, that normal guinea pigs exposed to highly vitiated air thereby acquire a slightly increased resistance towards the subsequent development of experimental tuberculosis.

4. We have failed to find that repeated drastic exposures of normal guinea pigs to vitiated air increased their liability to contract tuberculosis by contagion from infected animals. Such evidence as we have would indicate that such exposures are rather protective as measured by the susceptibility of control animals.

5. We could find no evidence that guinea pigs maintained on a diet containing a minimum of green food, and therefore deficient in vitamines, manifested greater susceptibility to the acquirement of tuberculosis by association with tuberculous animals than well-fed guinea pigs under similar conditions.

6. We have substantiated the proposition that "spontaneous tuberculosis" in normal guinea pigs may be expected to develop in an infected environment and in a degree somewhat proportional to the intimacy and duration of contact with tuberculous animals.

That there are factors which affect the predisposition of guinea pigs toward tuberculosis seems probable, but we have failed in our attempts to find them.

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BRONCHOPULMONARY SPIROCHETOSIS

DAVID T. SMITH[1]

As early as 1867 Leyden and Jaffe (52) discovered spirochetes in the sputum in cases of putrid bronchitis and also at necropsy in gangrenous lung tissue. Rona (80) in 1905 reported the presence of spirochetes and fusiform bacilli in two cases of pulmonary gangrene. The importance of these observations was not fully appreciated until Castellani's communication in 1906 (12). In Ceylon the latter observed two patients who seemed to be suffering with chronic pulmonary tuberculosis, but the absence of tubercle bacilli and the constant presence of spirochetes in large numbers in the sputum led him to conclude that he was dealing with a spirochetal infection, and he designated the condition *bronchial spirochetosis*.

Bronchial spirochetosis was considered a tropical disease until 1918, when Voille (93) (94) (95) (96) recognized the condition in the military and civil population of France. Since that time cases have been reported from nearly all parts of the world (table 1).

In the tropics, apparently, acute bronchial spirochetosis is caused by spirochetes alone, but in the chronic forms of the disease fusiform bacilli may be associated with the spirochetes (Castellani,[2] Chamberlain (16) (17) and Delamare (23)). In the temperate zones the fusospirochetal combination is, with few exceptions, a constant finding. Thus the necropsy reports of Feldman, 1906 (32), Kuster, 1907 (47), Muhlens, 1907 (64), Buday, 1910 (7) and Arnheim 1911 (2), comprising a total of 40 cases of pulmonary gangrene, pulmonary abscess and chronic bronchiectasis, showed spirochetes, fusiform bacilli and cocci in almost every instance.

The first recognized cases of spirochetosis or spirillosis of the lung in this country were reported by Johnson (42) in 1909. His patients were negroes; the disease was acute and terminated in spontaneous recovery. Rothwell (81) in 1910 reported three cases among whites which he called *bronchial Vincent's angina*. These patients also recovered after a number

[1] New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

[2] Personal communication to the author.

of weeks without specific treatment. Johnson and Rothwell made their observations independently of Castellani and of each other.

In the United States 107 cases of spirochetosis of the lungs have been reported (table 2), and in a subsequent communication an analysis of the bacteriological and clinical findings in these cases will be given. Suffice it to say that the morphological types of spirochetes encountered in this series were apparently identical; but the clinical manifestations were

TABLE 1

Geographical Distribution

COUNTRY	DATE OF FIRST REPORT	COUNTRY	DATE OF FIRST REPORT
Germany (52) (2) (8)	1867	Belgium (66) (67) (68)	1918
Austria (80)	1905	Peru (19) (78)	1918
Ceylon (12)	1906	Egypt (29) (30) (86)	1919
West Indes (6)	1906	Brazil (10) (39)	1919
Philippines (16) (17)	1908	Cuba (60)	1919
United States (42) (81)	1909	Netherlands (38)	1919
Hungary (7)	1910	Turkey (23)	1919
Africa (15) (28) (37) (87)	1913	Spain (21)	1919
Switzerland (34) (35)	1915	Argentina (90)	1920
Serbia (56)	1915	Hawaii (83)	1920
England (9)	1917	Russia (98)	1921
India (97)	1918	Siam (61)	1921
China (54) (31) (40)	1918	Norway (27)	1922
France (3) (4) (55) (57) (74) (82) (84) (92) (93) (94)	1918	Portugal (24) (25)	1922
		Indo China (23)	1923
Italy (26) (89)	1918	Venezuela (79)	1923
Salonica (88)	1918	Canada*	1925

* Personal communication to Dr. H. A. Bray from Dr. F. C. Neal, Peterboro, Ontario.

varied, and probably depended on the severity of the infection, the location and extent of the disease, and the resistance of the patient (table 3).

The 14 case-reports here presented illustrate the wide variety of pulmonary conditions in which we have found spirochetes, fusiform bacilli and cocci either in the pulmonary sputum or in the lung tissue. Bacteriological, pathological and experimental studies now under way indicate that these microörganisms play an important rôle in the etiology of certain pulmonary diseases.

PULMONARY GANGRENE

I am indebted to Dr. E. N. Packard for the clinical notes and to Dr. L. U. Gardner for the necropsy findings in the following case:

Case 1: Mr. B., age 39, gave an irrelevant family and past history. The present illness began with a slight cough, followed shortly by expectoration

TABLE 2

Cases in the United States

PLACE	YEAR	AUTHORS	NUMBER
Rosedale, Miss.	1909	Johnson (42)	3
Liberty, Mo.	1910	Rothwell (81)	3
Kansas City, Kans.	1910	Hall (81)	1
Cincinnati, O.	1911	Peters (70)	3
New York City	1913	Lamb and Paton (49)	1
New York City	1913	Soper (85)	1
Brooklyn, N. Y.	1918	Greeley (36)	2
Baltimore, Md.	1920	Mason (59)	1
Annapolis, Md.	1921	Bloedorn and Houghton (5)	3
New York City	1921	Kline (43)	3
New York City	1921	Fishberg and Kline (33)	1
Galveston, Tex.	1921	Levy (51)	2
Cleveland, O.	1923	Kline and Blankenhorn (45)	4
Chicago, Ill.	1923	Pilot, Davis and Shapiro (73)	5
Chicago, Ill.	1924	Rawson (77)	1
Chicago, Ill.	1924	Pilot and Davis (72)	32
Halstead, Kan.	1924	McNeil (63)	1
Philadelphia, Pa.	1924	Jackson (41)	2
Henderson, Ky.	1925	Marshall (58)	1
Cleveland, Ohio	1925	Kline and Berger (46)	16
Chicago, Ill.	1926	Pilot (71)	2
Toledo, O.	1926	Ramsey (76)	5
Ray Brook, N. Y.	1926	Smith*	14
Total			107

* Cases reported in this article.

which quickly became copious and foul. The constitutional symptoms were marked, the temperature ranging between 102° and 104°, and pulse from 130 to 140. Dr. Packard saw the patient after he had been ill for four weeks, and at that time his condition was critical. On physical examination the entire right lung appeared to be consolidated, with cavity-formation at the apex. The roentgenogram indicated the presence of a large cavity throughout the upper third of the right lung and a pyopneumothorax at the base. Thoracen-

tesis yielded a few cubic centimetres of foul purulent material, which was negative for tubercle bacilli, as were repeated examinations of the sputum. The clinical diagnosis rested between pulmonary abscess and pulmonary gangrene.

About six weeks after the onset of the illness the patient died. The necropsy report by Dr. Gardner of the Saranac Laboratory stated that a large ragged cavity occupied the upper two-thirds of the right lung. The destruction of the lung tissue was practically complete, except for a small area along the mesial border, where fragments of vascular and bronchial trunks were still discernible. The borders of the cavity were sharply defined, and there was no intermediate zone of inflammation between it and the normal lung tissue below. The left lung appeared normal. The tracheobronchial lymph nodes were moderately enlarged by inflammatory edema, but no trace of tubercle could be detected.

TABLE 3

Types of cases reported by the author

1. Pulmonary gangrene
2. Lung abscess following tonsillectomy
3. Lung abscess following extrapulmonary operations
4. Lung abscess complicating neoplasms of the lung
5. Lung abscess following the aspiration of a foreign body
6. Primary or spontaneous lung abscess
7. Unresolved pneumonias
8. Acute bronchitis
9. Bloody bronchitis
10. Putrid bronchitis
11. Chronic bronchiectasis
12. Any of the above mentioned types associated with pulmonary tuberculosis

Smears made from the necrotic inner wall of the gangrenous cavity exhibited large numbers of cocci, fusiform bacilli and spirochetes (*S. vincenti, T. macrodentum and T. microdentum*).

LUNG ABSCESS FOLLOWING TONSILLECTOMY

Dr. Charles C. Trembley kindly furnished me with the clinical notes on the following case of *Mr. H. S.*:

Case 2: Mr. H. S., age 21, developed a severe productive cough, with loss of weight and night-sweats following tonsillectomy in January, 1926. Dr. Trembley saw the patient six months later. He was somewhat emaciated and moderately febrile, and had frequent cough with about 60 cc. of mucopurulent sputum daily.

On physical examination there were dulness and râles in the midportion of the left lung posteriorly. The roentgenogram of the chest showed a dense, uniform, circular and sharply circumscribed shadow corresponding to the area of dulness. The leucocyte count was 11,500 and the differential count normal. Repeated examinations of the sputum were negative for tubercle bacilli.

The patient responded to rest treatment and gained 24 pounds. An onset of repeated copious hemoptyses, not controlled by palliative measures, led to an attempt to collapse the lung by artificial pneumothorax, which did not stop the hemorrhages. Thoracotomy was then performed, and the abscess incised and drained by Dr. E. S. Welles.

A smear made of the necrotic material from the abscess cavity, when stained by the Fontana method, showed spirochetes (*S. vincenti, T. macrodentum*), fusiform bacilli and cocci. Aerobic cultures on blood-agar plates were sterile, although both the anaerobic blood-agar plates and the anaerobic tube-cultures gave a luxuriant growth of a fusiform bacillus and a nonhemolytic streptococcus.

The patient continued to bleed and died a few days after the operation. Necropsy was not allowed.

Certain cases of lung abscess rupture into a bronchus, drain completely and heal spontaneously. In two such instances Pilot and Davis (72) stained the foul pus expectorated at the time of rupture, and found numerous spirochetes, fusiform bacilli and cocci.

LUNG ABSCESS COMPLICATING EXTRAPULMONARY OPERATION PERFORMED UNDER GENERAL ANESTHESIA

Case 3: Mr. P. S., no. 8,740, age 37, had a double herniotomy performed under ether anaesthesia in May, 1925. In ten days he lost 11 pounds, and developed a slight cough which gradually became more severe and productive. In November he had an hemoptysis of about 60 cc.

When admitted to the Sanatorium in January, 1926, he was thin, his lips were cyanosed, his fingers clubbed, his breath foul, his temperature 99.6° and his pulse 116. His cough was severe, and he expectorated 120 to 150 cc. of foul, mucopurulent sputum daily. Dulness and numerous râles were elicited over the right upper chest, and the roentgenogram showed a dense shadow with evidence of cavity-formation in this region.

The leucocytes were 13,275, with 73 per cent polymorphonuclears; the urine was normal, except for a trace of albumin; and the Wassermann was negative. The sputum, on standing, settled out into three layers; repeated examination and animal inoculation failed to disclose tubercle bacilli. The freshly washed sputum always contained an abundance of spirochetes (*T. macrodentum, T. microdentum, S. vincenti*), fusiform bacilli, cocci and elastic fibres.

The patient received four injections of neoarsphenamin (0.3, 0.45, 0.6 and 0.3 gm.) at weekly intervals and, although he improved temporarily, this treatment was suspended because of blood-tinged sputum. After the sputum was free from blood for two months, the treatment was resumed, but it was finally discontinued as the disease in the lung gradually increased.

Although neoarsphenamin treatment was not efficacious in this instance, cases of a similar nature have been reported in which recovery followed the administration of this drug (46) (58) (63) (72).

LUNG ABSCESS COMPLICATING PULMONARY NEOPLASM

Pilot and Davis (72) have reported tumors of the lung, complicated by a terminal fusospirochetal infection and the following case falls into this category:

Case 4: Mr. C. B., no. 8,655, age 42, in May, 1925, suddenly developed a severe pain in the upper part of the left chest. Eight weeks later, cough and expectoration began, and were followed by loss of weight and strength, fever and profuse night-sweats. The man entered the Sanatorium in October, 1925, and at that time was evidently quite ill, with temperature ranging from 101° to 103°, and pulse between 120 and 136. There was marked cyanosis and the fingers were clubbed.

The physical examination revealed marked dulness, with alteration of the respiratory murmur and numerous râles over the upper part of the left lung. On the roentgenogram a shadow, corresponding in density to the heart shadow, occupied the left apex and the inner two-thirds of the upper two interspaces. The rest of the left lung field, except at the extreme base, presented moderately coarse discrete mottling. The right lung-field was clear.

The leucocytes ranged between 40,000 and 60,000. The differential count was polymorphonuclear leucocytes, 88 per cent; small lymphocytes, 9 per cent; monocytes, 2 per cent; and eosinophiles, 1 per cent. The hemoglobin was 70 per cent.

The urine was normal, and the Wassermann and intracutaneous tuberculin tests negative.

The sputum, about 60 cc. in twenty-four hours, was frothy and mucopurulent, but not foul. It was repeatedly negative for tubercle bacilli by the usual methods of examination and by guinea-pig inoculation. Spirochetes (*T. macrodentum, T. microdentum, S. vincenti*), fusiform bacilli and cocci were found in the fresh sputum on eighteen occasions.

Blood cultures, taken on November 20 and 25, six months after onset, gave pure cultures of fusiform bacilli. This microörganism was also recovered from

the liver and kidneys of two mice, that died following the intraperitoneal inoculation of 0.5 cc. of the blood.

The patient did not respond to four injections of 0.4 gm. of neoarsphenamin, although the spirochetes permanently disappeared from the sputum. The diseased lung was collapsed to about one-third its original size by artificial pneumothorax, but owing to the grave condition of the patient the procedure was stopped. He developed toxic delirium, and was transferred to Bellevue Hospital in New York City in March, 1925, after a stay of six months in the Sanatorium.

Dr. James Alexander Miller made a diagnosis of neoplasm complicated by abscess, which was confirmed at necropsy.

SPONTANEOUS OR PRIMARY LUNG ABSCESS

Spontaneous lung abscess occurred in 22 of 60 cases reported by Lambert and Miller (48). Dr. W. B. Soper kindly furnished me with the clinical notes on the case of *Miss M.*, who may apparently be included in this group.

Case 5: Miss G. M., age 31, with an irrelevant past history, had her tonsils removed because of vague abdominal symptoms in March, 1925. Her convalescence was uninterrupted. Six months later she developed anorexia, lassitude and a slight nonproductive cough. There were no definite physical signs, but the roentgenogram presented a small, dense, circular shadow, about the size of a fifty-cent piece, in the centre of the upper third of the right lung field.

In November, six weeks after onset, the patient began to expectorate from 30 to 40 cc. of mucopurulent sputum, which was frequently blood-streaked. Repeated examination of the sputum and animal inoculation failed to reveal the presence of tubercle bacilli. On six different occasions I was able to demonstrate spirochetes (*S. vincenti*, *T. macrodentum*, *T. microdentum*), fusiform bacilli, vibrios and elastic tissue.

Treatment with sulpharsphenamin, iodides and bismuth did not benefit the patient. In July, 1926, she was referred for surgical advice to Dr. Adrian Lambert, who performed a thoracotomy, and incised and drained the abscess. Smears made directly from the abscess wall showed many spirochetes and fusiform bacilli. The patient is doing well at this time.

UNRESOLVED PNEUMONIA

In certain instances of unresolved pneumonia, spirochetes and fusiform bacilli are found in the sputum and in the lung at autopsy (72). It has

not been satisfactorily established, as yet, whether the fusospirochetal infection is primary or secondary.

Case 6: Mr. M. no. 8,515, age 17, developed in June, 1925, an acute respiratory infection accompanied by blood-streaked sputum, which his family physician diagnosed as pneumonia. After four weeks in bed, the cough became less severe and the appetite improved, but the sputum, which had been scanty at first, increased and became mucopurulent.

When admitted to the Sanatorium, one month later, the patient had a slight but persistent elevation of temperature (99.4°–99.6°), with frequent cough, productive of 60 cc. of mucopurulent sputum daily. The chest roentgenogram was normal, and the physical examination negative except for medium-sized râles at both bases.

The urine was normal, leucocytes 5500, and hemoglobin 80 per cent. Repeated examinations of the sputum failed to reveal tubercle bacilli. However, spirochetes (*T. microdentum, S. vincenti*), fusiform bacilli, cocci and elastic tissue were constantly present.

The patient failed to react to the intracutaneous test with 0.1 mgm. O.T.

He was given five doses of neoarsphenamin (0.15, 0.3, 0.45, 0.6, 0.6 gm.) intravenously at weekly intervals, and at the same time potassium iodide by mouth (5 gr. *t.i.d.*) for five weeks. After the second injection the temperature became normal. The sputum increased subsequent to the first two injections and then rapidly decreased. The spirochetes and elastic tissue disappeared following the third treatment, the râles after the fourth, and the expectoration ceased entirely after the fifth.

He was discharged in December, 1925, free from signs and symptoms of pulmonary disease.

ACUTE BRONCHITIS

Spirochetes are present in certain cases of acute bronchitis. In two cases reported by Chevalier Jackson (41), ulceration of the bronchial tree was observed with the bronchoscope, and smears made directly from the lesion showed large numbers of spirochetes and fusiform bacilli. One of these patients was recovering from a Vincent's angina of the mouth; the other gave no history of a mouth infection. During an epidemic of Vincent's angina among the Canadian troops stationed in England, Campbell and Dyas (9) reported 7 cases of acute bronchitis, in which mouth lesions were absent, but the sputum of which contained large numbers of spirochetes and fusiform bacilli. The patients recovered spontaneously after a few weeks of rest and the administration of a simple expectorant.

The following case also developed without evidence of mouth infection:

Case 7: Miss O. N., no. 8,699, age 16, developed in August, 1925, a non-productive cough which lasted for several weeks, and as one of her sisters had been treated for tuberculosis she was admitted to the Sanatorium for a period of observation. Several examinations at the Sanatorium failed to disclose evidence of pulmonary disease.

A few months after her admission she suffered from an acute bronchitis, when she was slightly febrile for a few days, but she was otherwise quite comfortable except for a productive cough which continued for about three months. Her physical signs were those of bronchitis, with numerous râles at both bases.

The sputum, mucopurulent and occasionally blood-streaked, was negative for tubercle bacilli by microscopic examination and animal inoculation. Large numbers of spirochetes and fusiform bacilli were constantly present in it for four weeks before the administration of neoarsphenamin. Two courses of the drug, of six injections each, given during three months, resulted in the cessation of cough and expectoration. Although complete recovery occurred in this instance, one cannot reasonably attribute the result solely to the neoarsphenamin, inasmuch as spontaneous healing is frequent in this condition.

BLOODY BRONCHITIS

The constant expectoration of bloody sputum without evidence of pulmonary consolidation is the striking symptom in certain cases reported by Rothwell (81), Lewis (53) and Bloedorn and Houghton(5). Rothwell's cases cleared spontaneously, Lewis's with arsphenamin, and Bloedorn's and Houghton's with neoarsphenamin treatment.

Bloody bronchitis is the clinical type of spirochetal infection most frequently encountered in the tropics (1) (28), (37) (62).

Case 8: Miss H., age 31, with family history of tuberculosis, suffered from a transitory pleurisy on the left side in 1920. Four years later she expectorated 15 cc. of blood. The following year she had an attack of "influenza," with pain in the right side of the chest, cough, and the expectoration of a slight amount of bloody sputum. For the next two months the sputum almost daily contained laked blood varying in amount from 5 to 20 cc.

There was no evidence of a pulmonary lesion either by physical or roentgenographic examination. The sputum repeatedly contained polymorphous spirochetes, fusiform bacilli and cocci. Tubercle bacilli were not found by either direct examination or animal inoculation. The blood count was normal and the Wassermann test negative.

The patient made a satisfactory recovery without specific treatment.

The following case of bloody bronchitis ran a much more protracted course:

Case 9: Mr. T. H., no. 8,635, age 40, four months after an attack of "influenza" in April, 1924, from which he apparently recovered, noted that his sputum was blood-streaked. A few days later he had an hemoptysis of 30 cc. and entered the Fordham Hospital. He remained there two weeks, expectorating daily 20 to 30 cc. of bloody sputum, which he said resembled red ink.

After being discharged from the Fordham Hospital he entered the New York City Sanatorium at Otisville, where he remained for ten months, and although his general condition improved, the cough continued and the sputum was occasionally blood-tinged.

When admitted to the New York State Hospital at Ray Brook in October, 1925, his only symptoms were cough and expectoration. Routine physical and roentgenographic examinations were negative. After intratracheal injection of lipiodol, definite evidence of bronchial disease was found at the base of the left lung posterior to the heart.

The urine and blood were normal, and the Wassermann test negative, as were microscopic examination and animal inoculation for tubercle bacilli. The mucopurulent sputum, particularly when blood-streaked, contained large numbers of spirochetes (*S. buccalis, T. macrodentum, T. microdentum, S. vincenti*), fusiform bacilli and cocci.

After two courses of neoarsphenamin, the sputum has been reduced from 60 to 20 cc., and, although it is still occasionally streaked with blood, the spirochetes and fusiform bacilli have disappeared.

CHRONIC IDIOPATHIC BRONCHIECTASIS

Included among the conditions leading to chronic bronchiectasis are a group of apparently unrelated pulmonary diseases in which spirochetes have been repeatedly recovered from the sputum, indicating the possibility that these diseases may have a common etiology.

CHRONIC BRONCHIECTASIS WITH INSIDIOUS ONSET

Case 10: R. R., no. 8,506, age 18, had a slight pain in the upper part of the left chest, with slight cough and expectoration in April, 1924. He did not feel ill, and in August entered the training camp at Plattsburgh. After three weeks in camp, his expectoration increased to 30 cc. daily and was mucopurulent. He returned home in September. The pain in the chest recurred for a short time, the cough became more severe, and the expectoration, copious and foul, amounted to 200 cc. daily. However, the patient felt fairly well, and

continued working as a machinist's helper until July, 1925, when he entered the Sanatorium. He was well-nourished but slightly febrile, and his fingers were definitely clubbed. Physical examination revealed numerous medium and coarse râles confined to both bases. The roentgenogram showed an increase in the number and density of the linear markings in the lower portion of both lung fields, which were otherwise clear; that taken after an intratracheal injection of lipiodol showed bronchial dilatations confined to the left base.

The urine was normal, the Wassermann test negative, and hemoglobin 80 per cent, while the leucocytes varied from 13,600 to 21,000. The differential count was 80 per cent polymorphonuclear leucocytes, 7 per cent lymphocytes, 3 per cent large lymphocytes and 10 per cent monocytes. Ten consecutive examinations of the sputum were negative for tubercle bacilli, as were the inoculations of the sputum into guinea pigs on two different occasions. Numerous fusiform bacilli and cocci were present in the sputum. Spirochetes were consistently absent until January, 1926, when they were discovered following an acute attack of pleurisy accompanied by a sharp febrile reaction and blood-tinged sputum. Afterward, for six weeks, spirochetes were constantly present in the washed sputum.

With the aid of postural drainage, begun September, 1925, the patient's general condition improved, and the sputum lessened appreciably and lost much of its foul odor. At this time, the patient received six injections of neoarsphenamin (0.3, 0.45, 0.45, 0.6, 0.6, 0.6 gm.) weekly. After a period of six weeks, a second course of neoarsphenamin was administered. The patient gained nine pounds, and the amount of sputum was reduced from 200 to 30 cc. daily, and on repeated examinations no spirochetes were discovered for three months, at the end of which time the patient was discharged from the institution.

BRONCHIECTASIS FOLLOWING ACUTE RESPIRATORY INFECTIONS IN CHILDHOOD

Chronic bronchiectasis is not infrequently a sequel of acute respiratory infections in childhood, particularly whooping cough and the respiratory complications of measles.

Case 11: Miss W., no. 8,684, age 23, a telegraph operator, suffered from chronic cough with mucopurulent expectoration, varying from 30 to 90 cc. daily, since an attack of measles in early childhood. The patient says that during this period she felt fairly well and was in good nutrition, and was a regular attendant at school and at work except when she was ill with so called grippe. A friend of the patient, a nurse, suggested that she consult a physician because of the cough and expectoration, and following this examination the patient came to us in November, 1925, for a period of observation.

She appeared healthy, and her only complaints, were cough and expectoration. Physical examination disclosed numerous râles confined to both bases; the routine roentgenogram failed to show evidence of disease, but those films taken following an intratracheal injection of lipiodol revealed unmistakable evidence of moderate dilatations of the bronchi at the left base.

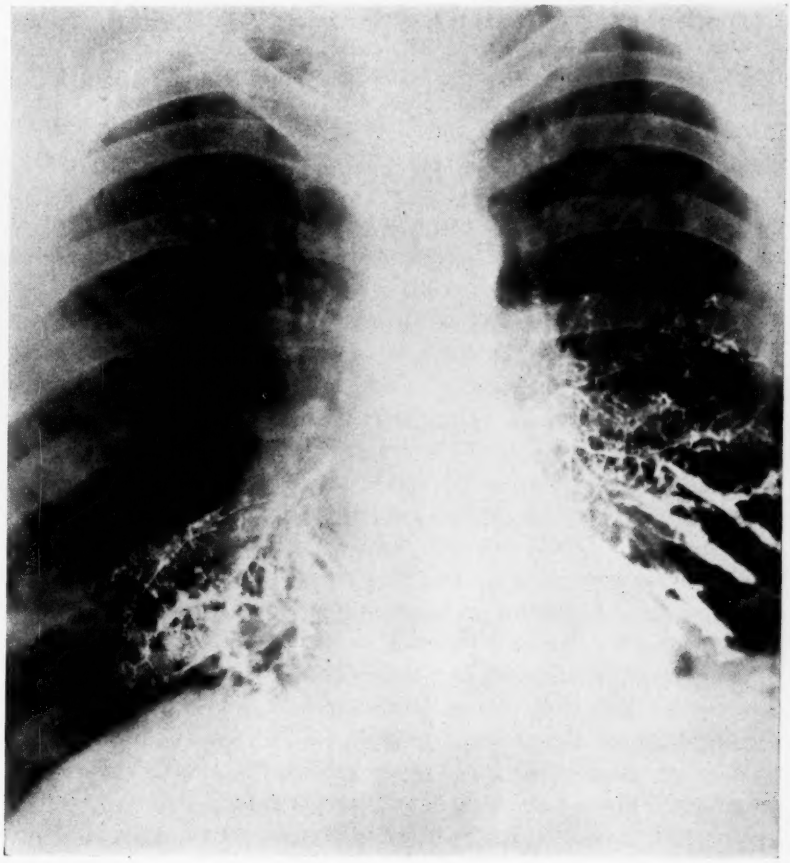

FIG. 1. CHEST ROENTGENOGRAM OF A PATIENT WITH BRONCHIECTASIS AFTER THE BRONCHI HAD BEEN INJECTED WITH LIPIODOL BY THE SUPRAGLOTTIC METHOD DESCRIBED BY PRITCHARD (75)

Postural drainage revealed that the patient's bronchi held two ounces of residual sputum

The blood and urine were normal, the Wassermann test doubtful on several occasions, and repeated examinations of the sputum and animal inoculation were negative for tubercle bacilli. Spirochetes (*S. buccalis and S. vincenti*), fusiform bacilli, cocci and vibrios were constantly present.

Postural drainage was begun in January, 1926; and a month later a course of neoarsphenamin was administered, followed by a course of sulpharsphenamin in April. Gradually the cough has been allayed and the amount of sputum reduced from approximately 80 to 30 cc. daily, and for the past few months spirochetes have not been found in the sputum. Fusiform bacilli and cocci are still present in small numbers, although the patient is in excellent general condition and working.

CHRONIC BRONCHIECTASIS FOLLOWING INFLUENZA

Case 12: Mr. P. J., no. 8,219, age 46, complained of cough, expectoration and lassitude following an attack of influenza during the epidemic of 1918. He continued to work until the summer of 1923, when he developed a paroxysmal cough, and the sputum which was previously mucoid became mucopurulent, copious (about 300 cc. daily), and occasionally blood-tinged. Several examinations were negative for tubercle bacilli.

The patient appeared healthy, and was afebrile when he came to the Sanatorium in December, 1924. He complained then of severe cough and frequent expectoration. His fingers were clubbed, and his chest barrel-shaped and hyperresonant on percussion. There were medium and fine râles at the base of the right lung posteriorly. The roentgenogram also showed honeycomb-like shadows at the right base. The urine and blood were normal. The sputum was thick, green, mucopurulent and slightly foul, and settled out in three layers on standing. It was frequently blood-streaked, and at times contained laked and partly digested blood resembling prune juice. Examination of 18 different specimens of sputum and the inoculation of 3 guinea pigs failed to demonstrate tubercle bacilli. However, spirochetes (*S. vincenti, T. macrodentum*), fusiform bacilli, cocci and elastic tissue were constantly present in large numbers. The sputum was blood-streaked almost daily for the first three months during the patient's residence in the Sanatorium, and on one occasion he expectorated 30 cc. of bright red blood. During this period his temperature did not rise above 99.2° and the patient felt well.

Beginning in April, 1925, he received five intravenous injections of neoarsphenamin (0.3, 0.6, 0.2, 0.6, 0.4 gm.) at weekly intervals. Shortly after the last treatment, his sputum diminished and was free from spirochetes, blood and elastic tissue, but the fusiform bacilli persisted. When the sputum became entirely free from blood, the patient was treated by postural drainage, without obvious improvement. Blood-tinged sputum occurred during postural drainage, and the sputum again contained spirochetes, which, however, disappeared after the second course of neoarsphenamin. Potassium iodide, gr. v, *t.i.d.*, was administered, but was discontinued after two weeks because of noticeable increase in the amount of sputum. At the time the patient was discharged,

in October, 1925, after a period of ten months' treatment, there was no definite change in the physical or roentgenographic findings.

Six months after leaving the Sanatorium the patient wrote that his sputum was free from blood and that he was feeling quite well and able to do a little work.

CHRONIC BRONCHIECTASIS FOLLOWING ABSCESS

Case 13: Mr. M., no. 7,525, age 19, was thoroughly chilled after falling through the ice in November, 1922, and within a few days he became feverish and developed a severe nonproductive cough. For the next month he felt rather badly but was not in bed. Then he had an hemoptysis of about 60 cc., followed by chills, night-sweats, marked fatigue, pain in the chest and considerable loss of weight. The cough was aggravated, and he began to expectorate about 30 cc. of mucopurulent sputum, which at times was blood-streaked.

The patient came to the Sanatorium in December, 1923, a little more than a year after the onset of his illness. He was in good general condition. The fingers were slightly clubbed. His sole complaint was a severe cough, amounting to from 100 to 150 cc. of foul mucopurulent sputum daily. On physical examination there was definite dulness at the base of the right lung, with medium coarse and sibilant râles. The chest roentgenogram disclosed a very dense shadow fusing internally with the heart shadow and projecting outward for a distance of approximately half an inch.

Tubercle bacilli were not demonstrated in the sputum by repeated examinations and animal inoculation. The sputum was not examined for spirochetes at that time.

The patient was appreciably benefited by postural drainage, the sputum being reduced to about half the amount but remaining foul. He returned home on April 22, 1924, with his condition improved. He continued postural drainage for the next year, but with no noticeable decrease in the amount or foulness of the sputum. At this time spirochetes were found in the sputum, and he was given two series of neoarsphenamin injections. Following this treatment, the sputum was reduced to 10 or 15 cc. daily, and entirely lost its foul odor, but spirochetes, fusiform bacilli and cocci were still present. At this writing, the patient's condition is satisfactory and he is employed at the Sanatorium.

CHRONIC BRONCHIECTASIS ACCOMPANYING PULMONARY TUBERCULOSIS

Case 14: Mrs. R., no. 6,569, age 23, suffered from chills and fever following exposure to inclement weather in October, 1918, and a few days afterward had an hemoptysis of 30 cc. Her temperature quickly returned to normal,

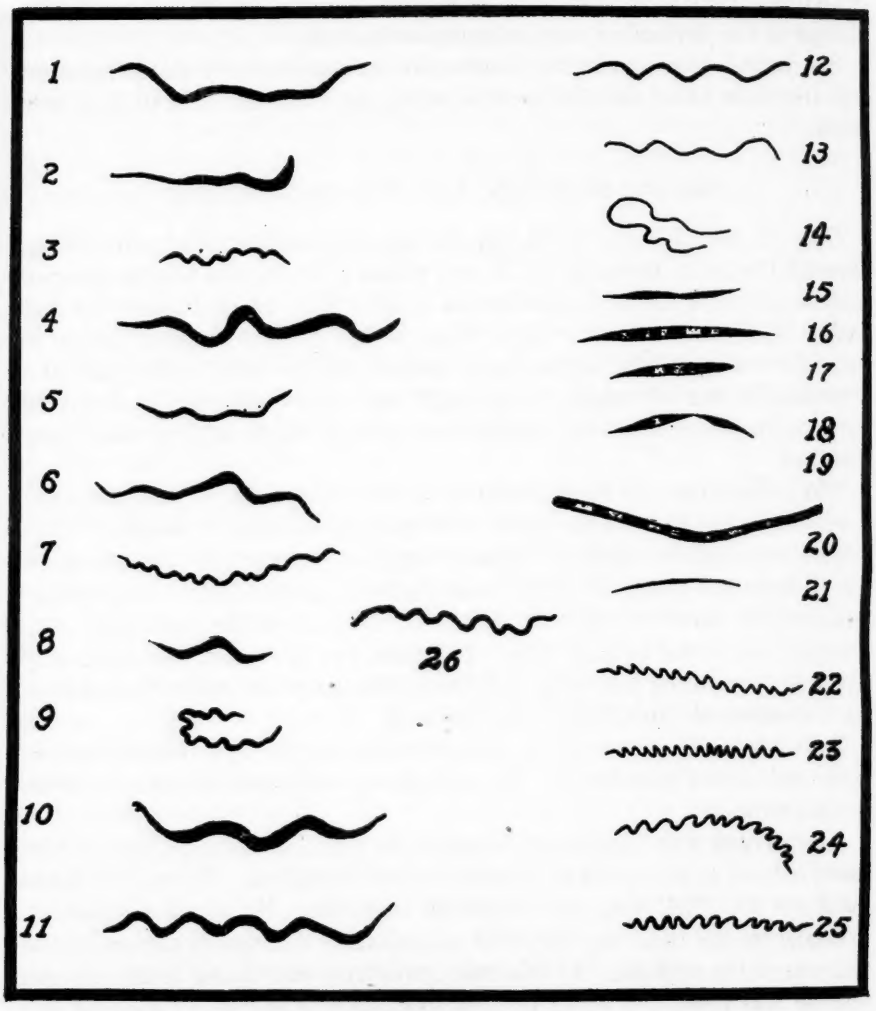

FIG. 2. CAMERA LUCIDA DRAWING OF SPIROCHETES AND FUSIFORM BACILLI

1 to 11: (Fontana stain) Illustrates the types of spirochetes found in the bloody sputum of a case of bronchiectasis

12: (Gram stain) Shows spirochetes and fusiform bacilli from the same specimen

22 to 25: (Levaditi stain) *Treponema pallida* from a section of a foetal liver, introduced to show the difference between the spirochetes found in bronchiectasis and abscess and those in syphilis

26: (Levaditi stain) Spirochetes from a section of an adult lung suspected of being syphilitic. It is seen that this microörganism resembles *3, 7* and *9* rather than the *treponema* in *22* and *25*

and she resumed her occupation as machine operator a week after the hemorrhage. However, her cough continued, and the expectoration gradually increased to approximately 100 cc. daily, and was occasionally blood-streaked and foul. These symptoms were present at the time the patient was admitted to the Sanatorium in November, 1921.

Her general condition was satisfactory. She was slightly febrile and the fingers were clubbed. Physical examination revealed definite signs at the base of the left lung, as well as evidence suggestive of disease at the right apex. The roentgenogram was negative, except for slight mottling at right apex. The patient responded well to Sanatorium treatment; her general condition improved and the sputum, formerly 30 to 40 cc. daily, was reduced to a few cubic centimetres, but was periodically blood-streaked. At this time she had an hemoptysis of one ounce, subsequent to which her cough became aggravated, her expectoration increased and her general condition suffered appreciably. She was discharged in December, 1922, with her condition unimproved.

One and a half years later, in June, 1924, she was readmitted to the Sanatorium. The physical and roentgenographic examinations showed no striking departure from the findings in 1922. However, the cough at this time was severe and the expectoration, mucopurulent and foul, was approximately 120 cc. daily and frequently blood-tinged. The examinations of the blood and urine were normal, and the Wassermann test negative. Although 26 examinations of stained preparations of the sputum over a period of three years were negative for tubercle bacilli four of five guinea pigs inoculated with the sputum during this period developed widespread tuberculosis.

Numerous spirochetes, showing great variations in size and shape, a few fusiform bacilli, cocci and vibrios were present in the sputum (figure 2). Intratracheal injections of lipiodol disclosed evidence of bronchial dilatations confined to the base of the left lung, identical in appearance to those observed in uncomplicated chronic bronchiectasis. The patient was treated successively by neoarsphenamin, tartar emetic and bismuth, but these therapeutic agents were ineffectual in freeing the sputum from spirochetes.

COLLECTION AND EXAMINATION OF THE SPUTUM

Precautionary measures are required to prevent the contamination of the sputum with the spirochetes commonly found in the mouth, particularly in the presence of pyorrhea. To this end the teeth should be thoroughly brushed and the mouth rinsed several times with a sterile mouth-wash just before the collection of the specimen. The sputum should be examined immediately, because within a few hours the spirochetes disintegrate and disappear. However, if the sputum contains

blood, the spirochetes may persist for eight to ten hours. A portion of the sputum about the size of a bean is rinsed in five changes of saline or Ringer's solution. A piece of purulent sputum about the size of a pinhead is then removed from the centre and a very thin smear is made.

In our experience and in that of most American workers, fusiform bacilli have invariably accompanied the spirochetes. They do not disappear from the sputum as do spirochetes on standing, and are readily stained by gentian-violet, methylene-blue and carbol-fuchsin. Consequently it is advisable first to search for the fusiform bacilli. If they are found, the Fontana silver-nitrate method is then employed to stain the spirochetes. If the smears are thick, or the staining solution not freshly prepared, one may fail to demonstrate the spirochetes even when they are present. At times spirochetes may be absent, although fusiform bacilli are present in large numbers. Spirochetes may be successfully demonstrated with the dark field. With this method, one can readily distinguish by their motility true spirochetes from pseudospirochetes formed from hypertrophied flagella (65).

DISCUSSION

It is generally assumed that spirochetes and fusiform bacilli are secondary invaders. If this were true, we would expect them to be present in all forms of chronic pulmonary disease. However, in 150 cases of uncomplicated pulmonary tuberculosis, 6 cases of bronchial asthma and 5 cases of mycotic infection of the lung, spirochetes and fusiform bacilli were absent from the sputum on repeated examination.

The cases here reported indicate that there is a group of apparently unrelated pulmonary conditions in which spirochetes, fusiform bacilli and cocci are constantly present in the sputum. These microörganisms, at least in so far as I have been able to ascertain, are identical with those commonly present in the mouth, and from this we may conclude that the mouth is the probable source of the pulmonary infection. This view receives support from experiments now under way, in which pulmonary abscess and pulmonary gangrene have been produced in mice, guinea pigs and rabbits by intratracheal inoculations of material recovered from the gums of patients suffering from severe pyorrhea.

There is reason to assume that bronchial spirochetosis may be the cause of primary bronchiectasis. In all of the 12 cases of bronchiectasis so far examined by me, most of them confirmed by intratracheal inoculation

of lipiodol, spirochetes, fusiform bacilli and cocci were recovered from the sputum. Anatomically, the bronchus and artery are not unlike, both being abundantly supplied with elastic and muscular tissue.[3] The fusiform and sacculated bronchiectatic cavities may be compared to similar changes occurring in the arterial wall. Aneurysms, at least those encountered before middle age, are with few exceptions due to the *Treponema pallida*, which destroys the elastic and muscular tissues in the arterial wall. Likewise, it seems possible that the Vincent type of spirochetes causes bronchiectasis by destroying the elastic and muscular tissues of the bronchus. We have repeatedly demonstrated elastic but not muscular tissue in the sputum in bronchiectasis. Chevalier Jackson (41) recovered spirochetes from an ulcer involving the bronchial mucosa, and this ulceration may represent the initial step in the development of the disease. The marked improvement that occurs in some cases of bronchiectasis following neoarsphenamin treatment lends support to this view.

I wish to express my thanks to Dr. H. A. Bray, Superintendent of the New York State Hospital, and his staff: Drs. John Weber, A. H. Duerschner, R. C. McKay, R. E. Heimbach, D. R. Gordon, E. R. Templeton, J. L. Wilson and E. H. Levy, for assistance in the clinical study of these cases.

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AN ETIOLOGICAL AGENT IN BRONCHOMYCOSIS

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The budding fungi are becoming more and more important as etiological factors in disease. The fungus, which is the subject for discussion in this report, was isolated from the sputum of a suspected tuberculous patient. The diagnosis of tuberculosis had been made by the physician, but he was unable to obtain confirmatory reports from several different laboratories. A specimen of sputum was brought to this laboratory and, after bacteriological examination by culturing and plating, it was found to contain great numbers of cells of an organism having yeast-like colonies. No acid-fast microörganisms could be demonstrated by the most careful preparation of smears and prolonged microscopic examination after staining. This suggested that the budding fungus was the etiological factor in the original infection.

HISTORICAL

The organism in this case was similar to *Monilia albicans*, which was first named *Oidium albicans* by Robin (1) in 1847. He gave the following description of the organism:

> Filaments are simple or branched, extremely small, transparent, septate and are grouped in little tufts. Spores are small, simple and transparent. Filaments are interwoven in loose clumps, at first hairy, watery and white; then later a dirty yellow. The contents are slightly granular. The filaments are 0.004 mm. wide and 0.05 to 0.6 mm. long. From the smaller threads little spores are formed. The organism was found in the mucous membrane of the mouth, throat, and esophagus of nursing children and in infirm old people near the end of life.

This description, it should be pointed out, was given at a very early day, and is mainly of historical significance. The lengthy discussion with which Robin follows this brief characterization gives more definite data about his original organism.

In 1912 Castellani (2) called attention to certain common bronchial infections in Ceylon and to the microörganisms causing them. These, all fungi, were divided by Castellani into five groups: *Endomyces*, *Saccharomyces*, *Aspergillus* and *Pencillium*, *Streptothrix* and *Actinomyces* and undetermined fungi. The commonest was *Endomyces*, which he described as having round

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or oval yeast-like cells with some segments of mycelium. He found 12 new species of this organism, all differing from the common *Endomyces albicans* by failing to liquefy gelatine. It is doubtful whether gelatine liquefaction is a salient characteristic with which to create new species. Castellani's twelve species, all of which are named, differ from each other mainly by their fermentation of sugars which even Castellani admits is an inconsistent criterion.

Steinfield (3) isolated three types of organisms from the sputum of patients suffering from asthma and chronic bronchitis. He called them *Monilia*, *Cryptococcus* and *Endomyces*. The first included all of those not having asci, and forming "mycelial septate segments;" the second, those that had little or no mycelial formation; and the third, those that produced spores. His organisms were not, apparently, fatal to guinea pigs. However, vaccines and potassium-iodide treatments were quite beneficial to the patients, thereby suggesting that the microörganisms were the etiological factors involved.

DePotter (4) isolated *Monilia albicans* from a chronic case of bronchitis. Experimental animals were found susceptible to this organism, all contracting a generalized mycosis. The organism was recovered in culture from practically all of the organs. He explained the action of *Monilia* as due to the destructive action of the growth and not to the formation of a toxin. Philibert and Cordey (5) have reported a yeast infection resembling pulmonary tuberculosis. Tubercle bacilli were not found in the sputum but a yeast, *Saccharomyces granulatus*, was found. They obtained complete recovery with iodide and methylene-blue treatment.

Castellani (6), in a later paper, enlarged his classification of the organisms causing bronchomycosis. As etiological agents in bronchomoniliosis (bronchomycosis caused by *Monilia*) he names 10 different species of *Monilia*, differentiated by their fermentation of sugars. He found that many of his organisms isolated from sputum were not fatal to guinea pigs. Some of the organisms, however, caused a nodular condition in the lungs that was not fatal.

Rappaport and Kaplan (7) reported a fatal case of generalized *Torula* infection in which they believed the primary lesion was probably in the lung. This patient also had tuberculosis. Shaw (8) has more recently isolated an organism from a case of bronchomycosis. This was from a clinical case of tuberculosis, although tubercle bacilli were never demonstrated in the sputum, nor did guinea pigs contract tuberculosis after injection of the sputum. He suggested the name *Monilia richmondi* for his organism. From his preliminary report it seems that *Monilia richmondi* has, in general, the same characteristics as *Monilia albicans*, and could be regarded as identical with this species or a variety of this fungus.

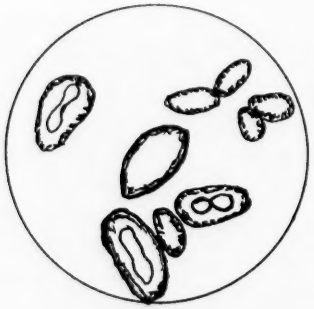

FIG. 1. CAMERA-LUCIDA DRAWINGS AFTER TWENTY-FOUR HOURS' GROWTH

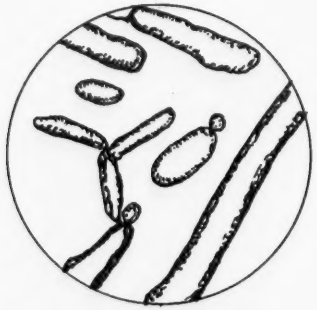

FIG. 2. CAMERA-LUCIDA DRAWINGS AFTER FORTY-EIGHT HOURS' GROWTH

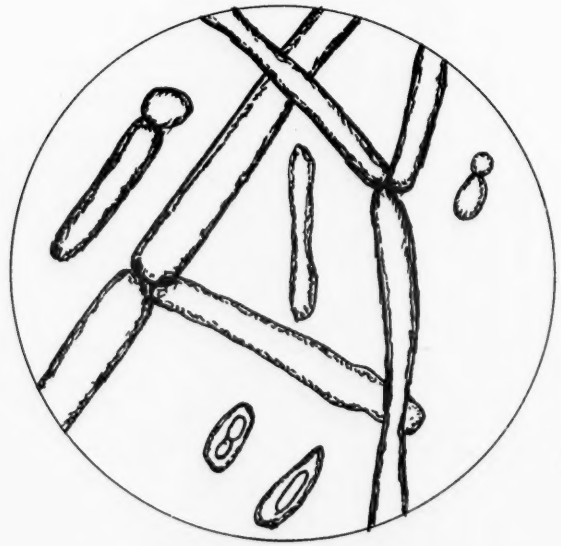

FIG. 3. CAMERA-LUCIDA DRAWINGS AFTER THIRTY DAYS' GROWTH

EXPERIMENTAL

The organism concerned in this report was studied for its morphological and cultural characteristics.

The cells were round or oval during the first day of growth in dextrose-broth, appearing as typical yeast cells. Mycelia began to develop in the sediment at the bottom of the tubes after about twenty-four hours, and were found throughout the medium after forty-eight hours. At first these mycelial segments were short, as if the yeast cell had merely elongated. However, they soon elongated more and more, until after thirty days there was quite a heavy mycelial growth and only a very few of the typical yeast-like cells. Camera lucida drawings are shown. No spores could be detected.

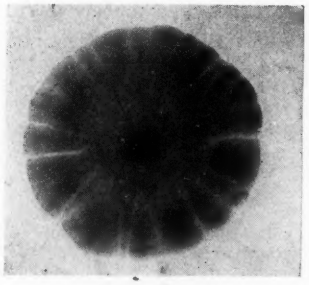

FIG. 4. GIANT COLONY

The growth on a dextrose-agar slant and a carrot slant was extremely rapid, covering the entire surface of the slant in about twelve hours. The appearance of the growth was dull white. The giant colony on a dextrose-agar plate was large and had the same dull white appearance. In liquid media there was a consistent granular pellicle and growth on the sides of the tube above the surface of the media. The liquid medium was heavily clouded, and a heavy precipitate formed in the bottom of the tubes.

The organism did not liquefy gelatin; it formed acid and curd in milk, and did not hydrolyze starch, reduce nitrates or form indol. It fermented glucose, levulose, and mannose, with the formation of acid and gas; dextrin, inulin, lactose, maltose, raffinose, sucrose and galactose, with the formation of acid only; and failed to act upon arabinose, glycerol, melizitose, rhamnose and xylose.

The organism was not fatal to experimental animals, although intra-

venous inoculation into a rabbit provoked a slight drowsiness; subcutaneous inoculation into a guinea pig produced a granular swelling at the point of inoculation. These animals were not killed and examined, so any chronic infection, due to the fungus, was not determined. This may not mean, however, that the organism is not pathogenic for man. Sheppe (9) found that only rats and mice were susceptible to *Torula*, and that experimental animals as a whole were resistant to these infections. Greenbaum and Klauder (10) also reported yeast infections, in which the causal organisms were found to be nonpathogenic for experimental animals. Ota (11) also reported many pathogenic yeasts as nonpathogenic for some experimental animals. Castellani and Steinfield also reported similar observations.

DISCUSSION

It is apparent from this report and reports in the literature that infections resembling clinical tuberculosis of the lungs may be caused by the budding fungi. The fungi responsible for these infections have been found to be members of several different genera, *Endomycetes*, *Monilia*, *Saccharomyces*, *Torulae*, etc. This suggests the advisability of searching for other parasites when the clinical symptoms of tuberculosis cannot be confirmed by laboratory examination. While the organisms have not always been extremely pathogenic, these infections have, in many cases as in the one reported in this paper, yielded to treatment with potassium iodide.

Attempts at identification and nomenclature of the budding fungi often lead to confusion. Craik (12) attributed some of the confusion to faulty interpretation of microscopic observations and the use of differences in fermentative ability as criteria for the creation of new species. He speaks of workers "who have given us a carefully devised scheme of sugar gymnastics which safeguards results, provided always we do not put an organism of which we know little into a sugar of which we know less." It seems easy for some investigators to create new species and thus make our knowledge more chaotic. The burden of proof ought to rest upon him who creates a new name and species, and not make other workers in the field prove that it is not a new species.

The fungus isolated in this investigation is believed to be *Monilia albicans* or a very closely related variety. It differs in none of the salient characteristics from this early species of Robin.

A comparison of the cultural characteristics of *Monilia albicans* as given by Castellani (13) with the characteristics of the organism reported here is given below:

	MONILIA ALBICANS CASTELLANI	MONILIA OF THIS REPORT
Litmus milk*	AC	AC
Gelatin liquefaction†	+	−
Indol	−	−
Glucose	AG	AG
Levulose	AGs	AG
Maltose	AGs	A
Galactose	AG	A
Saccharose	Avs	A
Lactose	−	A
Dextrin	−	A
Raffinose	−	A
Arabinose	−	−
Inulin	−	A

AC = acid and curd, *AG* = acid and gas, *A* = acid.

* Castellani says, "Several writers give it as clotting milk, others as having no action on this medium."

† Castellani says, "Some authorities state that the organism liquefies gelatin; others affirm the reverse."

Brom-thymol-blue was the indicator used in these tests for the determination of acid.

CONCLUSIONS

1. Certain yeast-like fungi cause a pulmonary infection greatly simulating clinical tuberculosis.

2. All cases of diagnosed clinical tuberculosis in which the laboratory findings do not confirm tuberculosis should be examined for fungus infections.

3. An organism, probably *Monilia albicans*, was isolated in this report from such a case. Potassium iodide greatly improved the patient.

4. Animal experimentation with these etiological agents may not prove their pathogenicity for man, as many of them are not pathogenic for the experimental animals commonly used.

5. The organism reported here differs in some respects from *Monilia albicans*, but not enough to establish a new species.

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THE BIOLOGY OF THE TUBERCLE BACILLUS

I. HYDROGEN-ION CONCENTRATION PRODUCED BY SOME MEMBERS OF THE GENUS MYCOBACTERIUM

JOHN WEINZIRL AND FLORENCE KNAPTON[1]

The present study is part of a larger problem, suggested by the Research Committee of the National Tuberculosis Association. It appeared worth while to compare the activities of the pathogenic with those of the saprophytic members of the acid-fast group of bacteria. Such a study may ultimately throw some light on the activities of microörganisms causing tuberculosis.

Extensive studies of the fermentative activities of the tubercle bacteria have already been made. In differentiating the bovine from the human type, Theobald Smith (1) in his memorable work showed that the reactions differed in glycerine-broth, the human developing a greater acidity than the bovine type. Griffith (2) of the British Royal Commission on Tuberculosis obtained similar results, but also found intermediate types and that the difference in acidity produced depended upon the luxuriance of growth, the slower-growing bovine producing less acid than the more rapidly growing human type. Lewis and Griffiths (3) found no marked biological difference between the two types, and Park and Krumwiede (4) confirmed their findings.

Grund (5) found that the human and bovine bacilli differed and he also observed microörganisms with atypical reactions. Wankel (6) likewise found exceptions to the rule. Frothingham (7), employing the potentiometer in his earlier study, found that the types differed but that exceptions occurred; he obtained different results on repeated tests of some strains. Later he (8) abandoned the potentiometer for the colorimetric method, adding the indicator to the medium before seeding. By this technique he obtained results similar to those found with the potentiometer, and he believed the method merited further trial.

Kendall, Walker and Day (9), in their metabolism studies on sapro-

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phytic human tubercle bacilli, found types intermediate between the human and bovine bacilli, but these tended to revert to one or the other on prolonged cultivation. They also found that these microörganisms produced a progressive alkalinity when grown in dextrose, mannite or plain broths; in glycerine-broth they gave acidity. Variations in the composition of the broth produced variations in the reaction curves of the same microörganism. Long and Major (10) grew the tubercle bacilli in amino acids, acid amines and ammonium salts, and found as a rule that they gave curves showing progressive alkalinity; if glycerine was also added, then the alkalinity was sometimes masked by the acid produced from it. Long, Campbell, and Smith (Miss Major) (11) did not believe that the bovine and human types could be differentiated by their fermentative activity because many bovine bacilli were marked acid-producers. They found that the same microörganism might differ quite widely in this respect when grown under apparently identical conditions. Fosca (12) studied various members of the acid-fast group on 4 per cent glycerine-broth. He found that *B. timothy* and the butter bacillus of Korn progressively acidified the medium from pH 8.1 to 6.5; *B. paraperlsucht*, from 8.1 to 7.9; *B. avian*, from 7.9 to 7.6; while *B. piscaire* raised it from 7.9 to 8.2. A human strain of *B. tuberculosis* grown on a synthetic medium containing asparagin acidified it from pH 7.0 to 6.3 in 30 days.

Summary of previous findings: Apparently investigators have been interested chiefly in the differentiation of bovine and human tubercle bacilli. For this purpose they have employed glycerine-broth, a medium of uncertain and variable composition. The acidity was estimated by direct titration, by potentiometer and by various colorimetric methods. Lack of uniformity seems to characterize the results for species and strains. Relatively little work has been done on the saprophytic species. If any laws underlie the work they seem vague and uncertain. The differentiation of bovine from human bacilli by means of fermentation curves appears difficult or impossible, due to integrating forms.

Object of this research: In view of the uncertainty surrounding the topic it appeared worth while to repeat the work on a more extensive scale, with a larger number of species and strains, with more fermentable substances, and with modern technique. It was hoped that more uniform results might be obtained; that the question of differentiating species and varieties might be definitely settled; and that any principles or laws underlying the fermentative activity of the tubercle group might be revealed.

METHODS EMPLOYED

Medium: Long's synthetic medium (13) was chosen because of its known chemical composition and ready reproduction, and because it was more likely to give constant results. The substances added to the medium were either 1 per cent dextrose, 1 per cent lactose, 1 per cent mannite or 5 per cent glycerine. The high percentage of glycerine was used to make the results more nearly comparable to those obtained by others. Steam under pressure, 20 pounds for 10 minutes, which was found to change the pH less than intermittent streaming steam, was used for sterilizing the media.

Cultivation: The cultures were grown in 250 cc. Koch flasks on the surface of the synthetic medium for some weeks or months in order to accustom them to it. All incubations were at 37°C. Contamination of the cultures during the long periods of incubation was avoided by inverting small beakers over the mouths of the flasks. Contamination was detected by a clouding of the medium, by variations in the duplicate flasks, and by stained microscopic preparations. Duplicate cultures and a blank control were always made.

Titration: The pH was determined by the technique of Clark and Lubbs (14) and the use of a *Lamotte Roulette H-Ion Comparator.* At intervals of two or three days, or longer for the slow-growing culture, 1-cc. samples were removed from the flasks under aseptic conditions for titration. It was felt that this procedure was more likely to give dependable results than the shorter method of incorporating the indicator in the medium and making direct readings.

MICROÖRGANISMS WORKED

A. Pathogenic:

a. Human (Mycobacterium tuberculosis (hominis) Koch):

1. H520, an avirulent strain received from the University of British Columbia. It grows abundantly on plain agar within 24 hours (chart I).

2. No. 115, from Michigan State Board of Health (chart II).

3. No. 117, from Mich. S. B. H. (chart III).

4. No. 1701 (H37) from A. T. C. C. The well known Hygienic Laboratory Strain (chart IV).

5. No. 1702, from A. T. C. C. (chart V).

6. No. 1703, from A. T. C. C. (chart VI).

7. No. 1705, from A. T. C. C. (chart VII).

b. Bovine (Mycobact. tuberculosis (bovis) Theobald Smith):

8. B525, an avirulent strain from University of British Columbia. Grows rapidly on plain agar (chart VIII).

9. B-A, Phipps Institute. After four months it was just beginning to grow on the surface of liquid media.

10. B-C, Phipps Institute. In four months just beginning to grow on liquid media.

c. Avian (Mycobact. avium, Straus and Gamaléia):

11. No. 407, received from Oregon Agriculture College (chart IX).

12. Avian III, Phipps Institute. After four months beginning to grow nicely on liquid media.

d. Piscine (Mycobact. piscium, Kral and Dubard):

13. Mycobact. piscium, received from Phipps Institute (A. T. C. C.). Failed to grow on liquid media.

B. Nonpathogenic:

14. Mycobact. butyricum (B. butter) from Phipps Institute (chart X).

15. Mycobact. berliniensis (B. butter, Rabinowitsch) from Phipps Institute (chart XI).

16. Mycobact. phlei (B. phlei (timothy)) from Phipps Institute (chart XII).

17. Mycobact. sterci (B. mist) from Phipps Institute (chart XIII).

18. Mycobact. graminis (Kervis grass bacillus) from University of Wisconsin (chart XIV).

19. Mycobact. smegmatis (B. smegmatis) from Phipps Institute (chart XV).

20. Mycobact. friburgiensis (B. butter, Korn).

We experienced considerable difficulty in making some of the pathogens grow on liquid media. Only after months of adaptation would they grow sufficiently for our work. Thus far several cultures have refused to grow. If a microörganism grew on glycerine-broth, it grew equally well on the synthetic medium. The failure to obtain satisfactory growth with some of the cultures has handicapped the work and limited the number of microörganisms we were able to study. The bovine and avian strains presented the greatest difficulty in this respect.

RESULTS OBTAINED

The data were recorded in tabular form, but for brevity and clearness they have been charted as curves (charts I to XV), all the results of one microörganism appearing in a single chart.

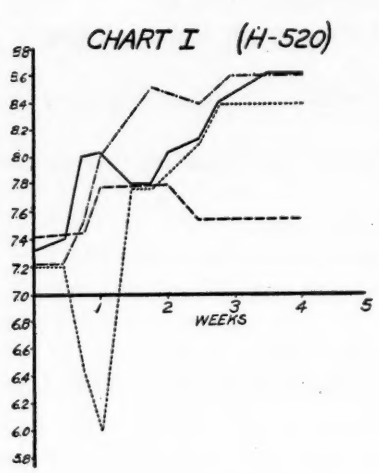


CHART I (H-520)
WEEKS

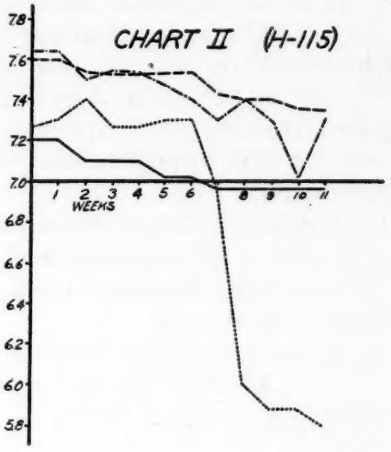


CHART II (H-115)
WEEKS

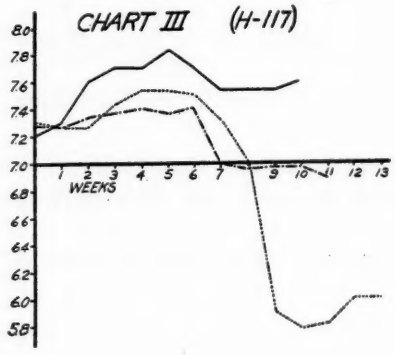


CHART III (H-117)
WEEKS

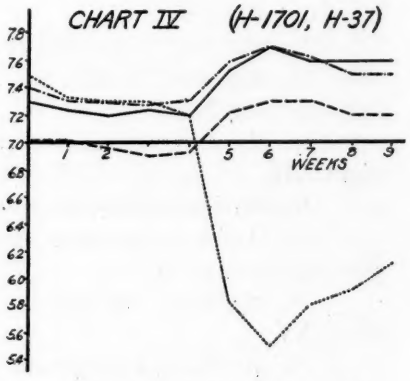
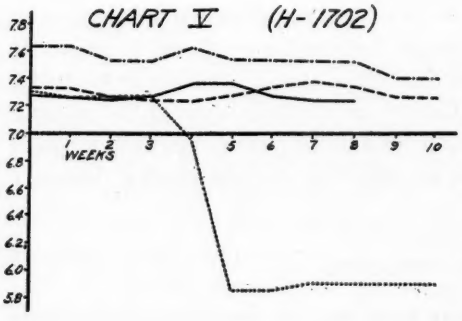


CHART IV (H-1701, H-37)
WEEKS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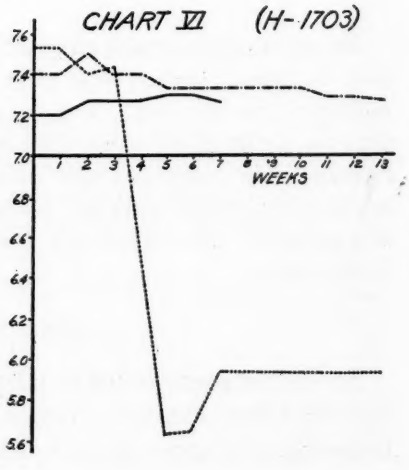
WEEKS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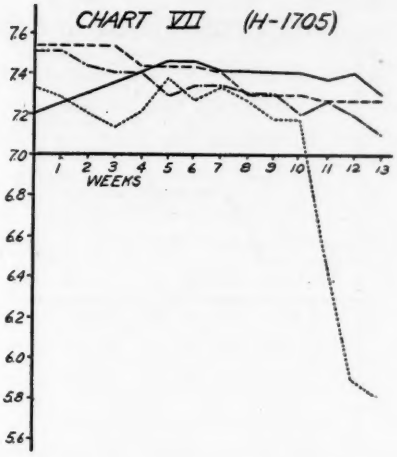
WEEKS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WEEKS

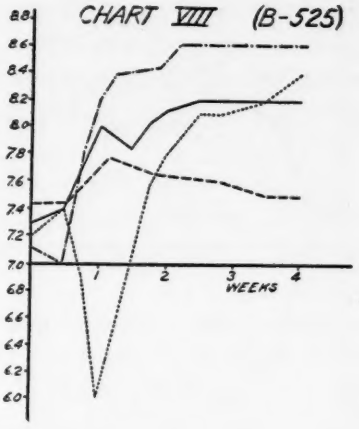


CHART VIII (B-525)
WEEKS

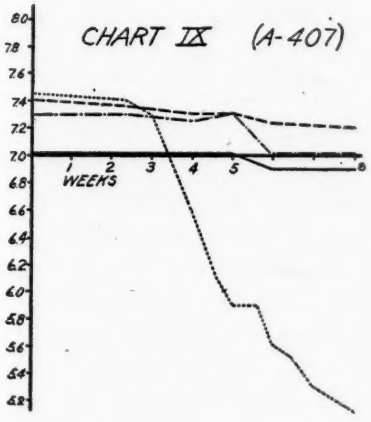


CHART IX (A-407)
WEEKS

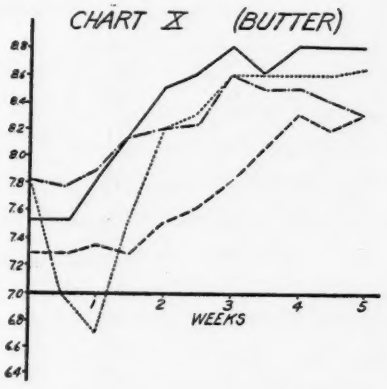


CHART X (BUTTER)
WEEKS

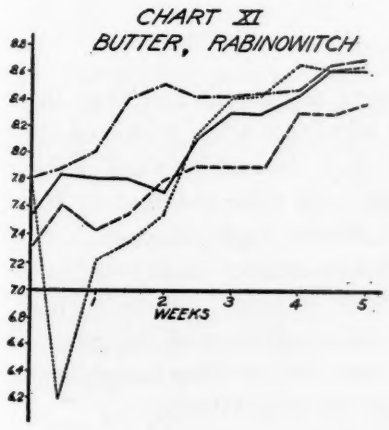


CHART XI
BUTTER, RABINOWITCH
WEEKS

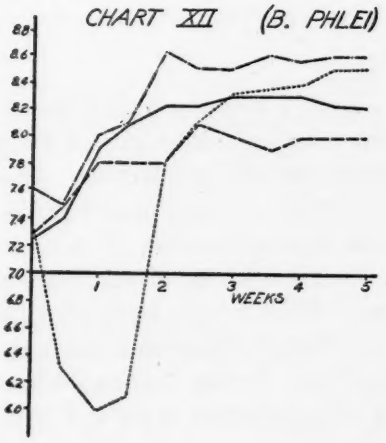
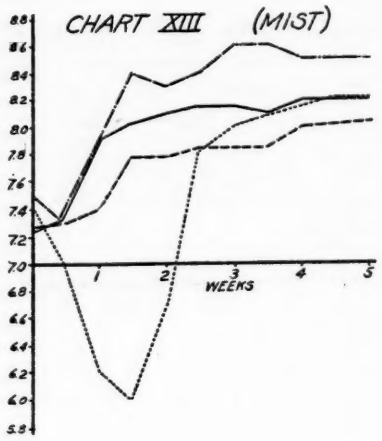
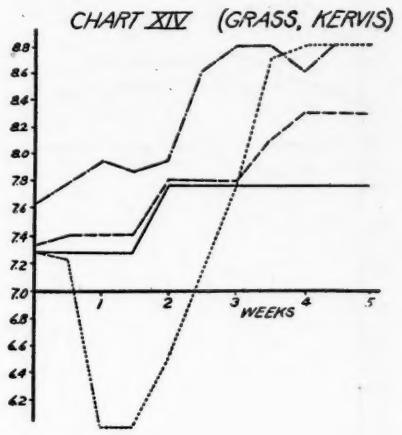
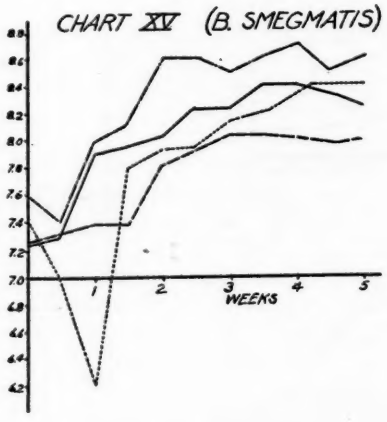


CHART XII (B. PHLEI)
WEEKS







DISCUSSION

Even a casual examination of the charts reveals the fact that all of the microörganisms gave a progressive alkalinity when grown on dextrose, mannite and lactose. Apparently they are unable to utilize these substances. These results are in harmony with those obtained by Kendall, Walker and Day (9), who, however, did not employ lactose.

On the other hand, all the microörganisms produced acidity on glycerine. These results agree with those of other workers. Glycerine therefore seems to play an important rôle in the metabolism of this group of bacteria. Frouin (14) and others claim that the bacteria use glycerine in the production of the wax which confers the acid-fastness.

Further observation of the charts reveals the fact that acid-production was directly related to the amount of growth; when the growth was most abundant acid-production was greatest. With slow-growers, the acid-production was delayed, while with rapid-growers it appeared early; this occurred regardless of whether human, bovine or other types were tested.

The glycerine-fermenters of this group divide themselves rather sharply into two subgroups; in one the acidity became permanent, while in the other it receded, and in some cultures became decidedly alkaline. This observation seems to be new.

A study of the two subgroups of glycerine-fermenters seems to show that those producing permanent acidity are virulent, while those showing recession of the acidity to marked alkalinity are avirulent. This observation may prove significant and seems not to have been made previously. Further studies are desirable to confirm this finding.

SUMMARY AND CONCLUSIONS

1. Fifteen species and strains of the acid-fast bacteria of the genus *Mycobacterium* were grown on a synthetic medium containing either dextrose, mannite, lactose or glycerine, and the pH curve was determined.

2. On dextrose, mannite and lactose all the microörganisms failed to produce acid; on the other hand, the alkalinity increased markedly.

3. On glycerine all the microörganisms produced acidity, and a direct correlation of acid production with growth-activity was found regardless of species or strains.

4. The glycerine-fermenters were of two types: in one the acidity became permanent; in the other the acidity receded, the culture finally becoming markedly alkaline.

5. The microörganisms which produced permanent acidity were virulent; those accompanied by a recession of the acidity to alkalinity were avirulent, regardless of species or strains.

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THE VARIABILITY OF THE LOCALIZATION OF TUBERCULOSIS IN THE ORGANS OF DIFFERENT ANIMALS[1]

V. THE SIGNIFICANCE OF LOCALIZATION AND DEVELOPMENT OF THE BACILLI, AND OF THE CELLULAR REACTION IN MAN AND ANIMALS

H. J. CORPER, MAX B. LURIE AND NAO UYEI

It is obvious that certain experiments will never be performed on man as they can be in animals. However, many deductions by inference are justified, on the basis of observations on many species of animals as well as on what is observed postmortem and clinically in man. In its localization in the animal, as well as in the human economy, tuberculosis has been prone to play almost freakish pranks. Therefore, no systematic deductions appeared justified to the majority of the earlier students of tuberculosis, regarding the localizations and development of the disease in man and animals or in their various organs. Even respecting pulmonary infection or disease, there is no unity of opinion as to whether it is accounted for by factors of localization, selective deposition, tissue susceptibility, or what not. A review of the commonly seen manifestations of tuberculosis in man will be presented in the light of our experimental studies on the guinea pig, rabbit, dog and monkey (1) (2) (3) (4). We shall also discuss the findings in these animals as they relate to each other.

There are many obstacles to drawing more than inferences from the human postmortem data available at present on tuberculosis of the various organs; and at least a few of the more important of these must be borne in mind when drawing conclusions on organic susceptibility to tuberculosis in man. If it is true that aerogenic infection predominates, then the preponderant pulmonary disease in man is a direct consequence of localization, and other factors may thus be overshadowed, so that they become indeterminable from human postmortem material (5). There might still remain the possibility of comparing the disease in the other

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

organs of the human body. But here again accurately recorded quantitative postmortem examinations are seldom available, for the usual autopsy is concerned little with the size of an organ from the standpoint of extent of morbid process, and the disease is roughly recorded as present or absent, or the organ designated as markedly or slightly involved, as the case may be.

However, some of these data are of value in elucidating the condition of organic susceptibility in man. Practically all figures agree that in adults pulmonary involvement predominates over that of any other organ; and, except for lymph-node involvement, this would also appear to be the case in children from the figures presented by Hand (6), Hedren (7), and Schwaitzar (8). Hand found 115 cases of tuberculosis in children among 332 autopsies, over a period of ten years in the Philadelphia Children's Hospital, and 78.3 per cent of the tuberculosis cases had pulmonary tuberculosis, this being the highest percentage for all the organs, and outstripped only by the bronchial lymph nodes, which had an incidence of 81.7 per cent. In this series the spleen showed an incidence of 47.8 and the liver 45.2 per cent, while the kidneys were involved in 22.6 per cent.

Hedren examined 47 children under one year of age, of which 26 presented only bronchial lymph-node and pulmonary lesions. The incidence of tuberculosis in this series was bronchial nodes 100 per cent, lungs 97.8 per cent, spleen 82.9 per cent, liver 61.7 per cent, and kidneys 34 per cent. Schwaitzar reports 724 autopsies on children 0–3 years old, with 72 presenting tuberculous changes. The organic involvement was 95 per cent for both the lungs and bronchial nodes, 62 per cent for the spleen, 45 per cent for the liver and 21 per cent for the kidneys.

As late as 1921 Robertson (9), in reporting on tuberculosis at postmortem, remarked that "frank tuberculosis of any organ or group of organs, aside from the respiratory tract, can hardly be arranged in any exact order." He believes that 50 per cent of all people of all ages have tuberculosis, and that next to the most common old healed pleuritis is evidence of old healed miliary tuberculosis of the lungs, spleen and liver. This is not so common in the lungs as in the spleen and liver, and of these two organs the nodules are more numerous and reach a larger size in the spleen. In a report on 50 autopsies of tuberculous subjects Warthin (10) states that in every case of pulmonary tuberculosis tubercles could be found in the liver. In the early stages they were small and scarce. In all the chronic cases the hepatic tubercles were more numerous, and

in many cases the picture was that of an acute miliary tuberculosis of the liver. The condition found in the spleen was always similar to that found in the liver of the same subject, with the tubercles small and scarce in the early stages, while in the more chronic cases they were more numerous and in many of the older subjects there was an acute miliary tuberculosis of the spleen. The kidneys contained tubercles in all cases of chronic pulmonary tuberculosis, but the lesions were always more scarce than in the liver and spleen. There was a 100-per cent incidence in the lungs, liver, spleen, kidneys, and larynx. As a result of microscopic as well as gross examinations, Rosenberger (11) found 83.8 per cent of 62 livers to contain miliary tubercles, 42 being positive for tubercle bacilli, and 97 per cent of the spleens (54 per cent positive for tubercle bacilli), from cases of chronic ulcerative pulmonary tuberculosis.

The questionable value of ordinary autopsy figures is well brought out by the annual autopsy reports from the Henry Phipps Institute. After recording in ordinary exhaustive fashion the reports of 143 cases for two years (12), the third-year report (13) attempts a more detailed presentation. It records the findings of 60 autopsies, all except 3 being far-advanced cases of chronic pulmonary tuberculosis. In the liver the tubercles were few in 28, moderate in one and numerous in two of 57 cases, there being miliary tubercles in 54.4 per cent of the cases, while histological tubercles were demonstrated in 38, or 70.3 per cent, of 54 cases. In the spleen miliary tubercles were found in 18 of 57 cases (31.5 per cent) on gross examination, while histological examination revealed tuberculosis in 68 per cent of the cases. The right kidney showed miliary tubercles in 36 and ulceration in one of the 57 cases, while the left kidney showed only miliary tubercles in 34 of the 57 cases and in none was there ulceration. Ullom (14) reported in detail the findings in the liver of the material from Phipps Institute and records finding tubercles microscopically 30 times, or 81 per cent, 21 with typical amd 9 with atypical lesions, in 37 cases. Schlapobersky (15) found tubercles macroscopically in the liver of about 10 per cent of tuberculosis cases at autopsy while microscopically they were found in 86 per cent of the cases examined, usually being located at the periphery of the lobule. Like Ullom he believes in a primary hematogenous infection.

The organ involvement in whites and negroes appears to differ slightly, according to Rogers (16), who examined postmortem 75 white and 75 negro tuberculous individuals. Whether age had any bearing on this is difficult to ascertain from the material presented, the average age of

the negro cases being 35 years and of the whites, 44 years. Tubercles were found in the liver of the negroes 31 times, the spleen 29 times and the kidneys 29 times, and in the liver of the white cases 24 times, the spleen 41 times and the kidneys 20 times.

Before evaluating these data further in the light of our animal findings, it appears important to bear in mind another factor—susceptibility—in human tuberculosis, which becomes apparent not only in racial differences to this disease but looms in the foreground when comparing the child with the adult. In the absence of accurate data only suggestions are possible. The little information that is available on children (17) would lead to the belief that they are fairly susceptible to inoculation infection with virulent human bacilli, yet in the light of the more recent clinical conceptions on the primary lesions and primary effect it would appear that even young children possess a decided degree of resistance to spontaneous infection with the human bacillus. They show a marked resistance to bovine infection if postmortem and clinical data are of significance. The adult is without doubt strikingly insusceptible to bovine tubercle bacilli and is only moderately susceptible to spontaneous infection with human bacilli if the chronicity of the average case of adult human tuberculosis is any index of resistance.

The previous four papers of this series have disclosed certain fundamental facts derived from the study of different species of animals, which can now be briefly reviewed and critically considered for the purpose of explaining organic susceptibility to tuberculosis in these animals before drawing upon them for evaluating organic tuberculosis in man, in so far as the data at present available would seem to permit.

It is evident from these studies on animals that the greatest amount of tuberculosis following the intravenous injection of living virulent human or bovine bacilli develops in the lung as compared to the other organs of the rabbit because in this animal there are two factors, the growth of the bacilli and the cellular reaction, which contribute to a maximum of disease in this organ, in spite of the fact that the localization of bacilli there is much less than in the liver or spleen. The oxygen tension, available in the lung for the growth of the bacilli, is greater than that in any other organ of the body, and this accounts in great part for the more rapid growth of the bacilli in the lung of the rabbit. In addition, the cellular factor, as indicated by the size of the tubercles developed in the lung of the rabbit in response to dead bacilli, is also favor-

able for maximum disease in this organ, since the phagocytic cells in the lung of the rabbit have the least power, of any of the organs developing appreciable disease after the intravenous injection of living virulent bacilli, of destroying the bacilli.

With regard to these two factors, the liver of the rabbit stands in an exactly opposite position to the lung. In this organ the oxygen tension is the lowest of any organ in the body and the cellular reaction is least, indicating that the Kupffer cells of the liver have a greater ability to destroy tubercle bacilli than any of the cells of the other organs developing appreciable disease after the intravenous injection of living virulent bacilli. Thus, even though many more bacilli localize in the liver than in the lung of the rabbit, little tuberculous involvement occurs in the liver following the intravenous injection of living virulent human or bovine tubercle bacilli, the tuberculous involvement being even less than in the kidneys, in which very few bacilli deposit under these conditions.

In the rabbit the rôle of the distribution of the bacilli after intravenous injection of living bacilli is prominent in the case of the spleen, kidney and bone-marrow, the number of tubercles developing in these three organs being in direct proportion to the amount of bacilli deposited in each. In these organs there is no fundamental difference in the ability of the bacilli to grow because the capillary blood has essentially about the same oxygen-supply tension. Though the tubercle-forming cells of the spleen are only slightly more capable of destroying tubercle bacilli than the tubercle cells of the lung, the lower rate of growth of the bacilli, due to the lower oxygen tension available in the spleen, overcomes this effect to such an extent that, in spite of the greater deposition of bacilli in the spleen, there results more tuberculosis in the lung of the rabbit.

In the guinea pig the cells of the tubercle of the spleen, of any of the organs in this animal developing an appreciable tuberculosis after the intravenous injection of living virulent tubercle bacilli, possess the least power to destroy tubercle bacilli, as is indicated by the cellular reaction to dead bacilli. In addition, the spleen of the guinea pig receives a greater number of bacilli per gram of tissue than any of the other organs after intravenous injection. These two factors combine to make the spleen of the guinea pig the site of most tuberculous involvement following the intravenous injection of living virulent human or bovine tubercle bacilli, even though the rate of growth of the bacilli in this organ is less than that in the lung, where the oxygen tension favors growth.

Since the cells of the tubercle of the lung and liver can destroy tubercle bacilli about equally well, as is indicated by the cellular reaction to dead bacilli, the importance of the growth of the bacilli, on the one hand, and the distribution of the bacilli after intravenous injection, on the other, assume importance in the determination of tuberculous involvement following the intravenous injection of living virulent human or bovine bacilli. During the first four weeks after infection the more rapid growth of the bacilli in the lungs accounts for the greater tuberculous involvement of this organ as compared to the liver, but later the factor of heavier seeding of the liver with tubercle bacilli predominates over the slower growth of the bacilli in this organ, and the tuberculous involvement then exceeds that in the lung. In the guinea pig tuberculosis rarely develops in the kidney, apparently because the number of bacilli deposited there after intravenous injection is too few.

In the dog the cellular reaction assumes a striking and significant importance. In the spleen, where more bacilli are deposited following the intravenous injection of living virulent human or bovine bacilli, there fails to occur any tuberculous involvement except after the intravenous injection of large amounts of bacilli, because the cells responsible for tubercle-formation in this organ possess a marked power to destroy the bacilli, as is indicated by the cellular reaction following the intravenous injection of dead bacilli. On the other hand, in the liver of this animal, where the deposition of bacilli is less and the growth of the bacilli is more retarded by the oxygen tension than in the spleen, there occurs an extensive tuberculous involvement following the intravenous injection of living bacilli because the cells of the tubercle (Kupffer cells) of this organ possess little ability to destroy the bacilli as is indicated by the cellular reaction to dead bacilli.

In the lung of the dog the factors of seeding and growth of the bacilli, as determined by the oxygen tension, account for the tuberculous involvement found after the intravenous injection of living virulent human and bovine bacilli. The tubercles in the lungs of the dog are the largest of those in any organ since the bacilli grow better in this organ because of the greater oxygen tension, and they are less numerous than in the liver because the seeding in this organ is less. The tuberculous involvement of the kidney and bone-marrow of the dog following the intravenous injection of the bacilli is accounted for by the deposition of the bacilli and their growth in these organs.

In the monkey, although the data obtained thus far are not as complete

or exhaustive as in the case of the other three species of animals, it seems that the larger size of the tubercles in the lung and the small size of those in the liver, following the intravenous injection, can be accounted for by the different oxygen tension of the source of oxygen of the cells of the tubercle in these two organs. In the monkey, a very susceptible animal to inoculation tuberculosis, an important part is also played by the distribution of the bacilli to the various organs, for in this animal those organs, except the lungs, are most involved where the bacilli localize to greatest extent after intravenous injection. The marked involvement of the bone-marrow and the cellular reaction in this animal have not been fully elucidated and remain for subsequent studies.

In summing up the observations on the four species of animals studied, it appears that in determining the tuberculous involvement of the organs, the oxygen tension of the source of oxygen is important in explanation of the greater tuberculous involvement of the lung as compared with the liver in all the species considered. In addition, the ability of the cells of the tubercle of the different organs to destroy tubercle bacilli, as expressed in the cellular reaction, assumes importance especially in explaining the irregular organic involvement not accounted for by the deposition or growth of the bacilli. The rôle of cellular reaction and the growth of the bacilli are relatively more important in tuberculosis in the resistant animals, like the rabbit and dog, while in the less resistant animals, like the guinea pig and monkey, the distribution of the bacilli assumes a more commanding position.

In the four species of animals studied, species susceptibility to the human and bovine strains of virulent tubercle bacilli can be correlated with the chemical constitution of the strain of tubercle bacillus in question, as related to the destructive power of the cells of origin of the tubercle in the various organs of the various animals for these bacilli (see table 4, study 4). The human bacillus contains less lipin than the bovine strain, and dead human bacilli are more readily destroyed by the phagocytic cells of the various organs of the rabbit than are dead bovine bacilli, which may in part explain the strikingly greater susceptibility of this animal to the bovine bacillus. The guinea pig being susceptible to both strains of tubercle bacilli, but slightly more so to the bovine, finds partial explanation in that the amount of tuberculosis developed in response to dead bacilli in the various organs is greater with bovine than with human bacilli, but this difference is not so marked as in the rabbit. Finally, the dog is equally susceptible to the bovine and the human strains of

living bacilli, and no marked difference in the size of tubercles in the same organs was noted with the dead bacilli.

DISCUSSION OF HUMAN TUBERCULOSIS IN THE LIGHT OF THE ANIMAL EXPERIMENTS ON ORGANIC SUSCEPTIBILITY

It is obvious from clinical and autopsy observations that pulmonary tuberculosis predominates in adult man and, though not usually stressed, the same appears to be the case in the child when lymph-node involvements are excluded from consideration. When attempting to explain the predominant pulmonary involvement in man on the basis of any preferred conception, a maze of controverting evidence is faced, which would seem to make the choice of a happy medium probably the safest. If the aerogenic route of pulmonary infection in tuberculosis is chosen, there remains little else necessary to explain the predominant pulmonary involvement and only surmises become possible. Probably the majority of students of tuberculosis have chosen this as the easiest way out and yet, with all fairness to the adherents of other views, it must be admitted that conclusive and indisputable proof is still lacking regarding the mode of infection in man. The possibility that the lungs are more favorably situated for the growth of tubercle bacilli on account of their higher oxygen tension than is any other organ in the body, has been given little, if any, consideration in the past, and yet the consistency of the findings regarding this in all the species of animals here studied makes it seem obvious that this factor plays a pertinent rôle in the predominant pulmonary involvement in tuberculosis in man. It is apparent that future autopsies on tuberculosis in man will have to give more consideration to quantitative relations, both macroscopic and microscopic, in so far as tuberculous involvement of the different organs is concerned, before organic tuberculosis in man can be adequately elucidated; and yet a survey of the postmortem data at present available may throw some light on the organic reaction to tuberculosis, especially when viewed on the basis of the reactions of the animals.

It is self-evident that suitable inoculation experiments may never be available for man, and only by a closer correlation of natural conditions in man with those produced experimentally in animals will it be possible to solve the intricacies of this disease as it is found in man. Fortunately, tuberculosis in the majority of cases of pulmonary tuberculosis in man apparently becomes generalized hematogenously, and this offers an

opportunity for fairly close comparison of the conditions resulting therefrom in man with those seen after hematogenous infection in animals. In this light it would appear that man more closely resembles the rabbit than the other three species of animals studied in organic reaction to tuberculosis, in that, considering seeding after hematogenous dissemination to be about the same as that found in the animals, the spleen becomes more involved than the liver and the kidney is least involved of these three organs. Certain reservations are, however, necessary in making these interpretations, in that the liver involvement more nearly approximates that of the spleen of man, making it seem likely that the lower oxygen tension of this organ in man is counteracted by a diminished ability of the cells of the tubercle of the liver of man to destroy tubercle bacilli as compared with the cells of the tubercle of the liver of the rabbit, and in that the kidney of man is less resistant to tuberculosis than the kidney of the rabbit, which is possibly also accounted for by the cellular factor. In man the relation to the strain of bacilli is reversed, for while all the animals tend to be more susceptible to the bovine strain, man reveals a remarkable resistance to this strain as compared to the human bacillus. Like the rabbit and dog, however, adult man displays a decided resistance to spontaneous disease, even to the human tubercle bacillus, which would also appear to be the case with the child in spontaneous infection, although apparently extremely susceptible to inoculation infection with virulent human bacilli. In the child these discrepancies require further elucidation, with probable eventual revision of conceptions.

These observations also emphasize the fact, so frequently seen in the laboratory, that it requires a certain minimum of tubercle bacilli to produce tubercle, just as it does for their growth on certain individual artificial media or to infect certain animal species, and in this each organ possesses its own individuality, which can, however, be brought into correlation with the cellular reaction, bearing in mind at the same time the importance of the growth of the tubercle bacilli as determined by the oxygen tension of the source of oxygen. Whether allergic conditions can alter these relations of organic susceptibility, or whether they will affect the body as a whole, remains for future observations to disclose.

SUMMARY

Among the factors controlling organic susceptibility to tuberculosis, there are preëminently:

1. The distribution of the bacilli to the various organs.

2. The growth of the tubercle bacilli in the organs of the body, as controlled by the oxygen tension of its source of oxygen.

3. The ability of the cells of origin of the tubercle in the various organs of the different species to destroy the tubercle bacilli, as is indicated by the organic cellular reaction.

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THE RELATION OF MILK TO TUBERCULOSIS[1]

WILLIAM H. PARK

The subject of this paper covers the extent of human tuberculosis due to the bovine bacillus and the practicability of reducing or eliminating it by the destruction of the tubercle bacilli in milk and milk products or by the elimination of the infection of milk by preventing tuberculosis in cattle.

The original discovery of the tubercle bacillus by Koch was later extended by the additional discovery that in diseased birds the tubercle bacillus differed in certain clearly defined characteristics from that of man. This difference was sufficient to separate it as a distinct type. Investigation proved that the avian type was not naturally communicated to man or cows and was chiefly of importance to birds.

In 1896 it was further discovered that the mammalian tubercle bacillus probably comprised two distinct types. Theobald Smith published a careful study on a culture from a pet animal believed to have derived its infection from a human source and on another culture from a tuberculous bull. He noted differences which were so definite that he concluded that more evidence as to the identity or nonidentity of bacilli from bovine and human sources was needed. He published further evidence in 1898 of the existence of a separate human and a separate bovine type of mammalian tubercle bacilli. In 1910 Koch corroborated these differences and made the statement, "In view of all these facts I believe that I am justified in maintaining that human and bovine tuberculosis are not identical, and that the human variety cannot be transferred to cattle." He stated, concerning the susceptibility of human beings to bovine tuberculosis, the following:

> This question cannot be answered directly, since, of course, experiments on human beings are not permissible; but we can get at a solution indirectly. It is a well-known fact that much of the butter and milk consumed in large cities contains a considerable number of living tubercle bacilli of the bovine type. If these are pathogenic to human beings, we ought to find among the inhabitants of large cities, who daily swallow these living, virulent organisms,

[1] An address on the sociological subject, *Milk and Tuberculosis*, delivered at the *Fifth Conference of the International Union Against Tuberculosis*, Washington, D. C., October 2, 1926.

and thus unconsciously carry out the very experiment which we could not undertake, many cases of tuberculosis that can be traced to food contaminated with the tubercle bacillus; especially ought this to be true in children. To-day we are able to determine the type of bacillus. It is necessary merely to isolate the organism from the tuberculous material in pure culture, and by inoculation into cattle establish whether it is of the human or the bovine variety. For half a year I have experimented along these lines, but, owing to the scarcity of material, have been able to examine only a few cases. So far results do not indicate the occurrence of bovine tuberculosis in man. I should be inclined to consider the number of cases of tuberculosis caused by milk, butter, or meat of tuberculous cattle not much greater than that of hereditary cases, and I believe, therefore, that no special protective measures are indicated.

Most of his examinations were made from material from adult cases. These views found opposition in most quarters. Numerous investigations followed. The resulting evidence left no doubt of the infectiousness of the bovine virus for children, but in the case of adults Koch's opinion was corroborated.

The importance of the question from the human standpoint rests on the percentage of such infection. The prevention of tuberculosis in cattle, without regard to its influence on human tuberculosis, is important for the welfare of the cattle and from a purely commercial standpoint. If, however, bovine tuberculosis is a menace, that is, causes an appreciable percentage of the tuberculosis in man, this involves the production of milk and its products free from any infectious material or, if this is impracticable, the destruction of the bacilli in the milk before it is consumed. With a milk supply such as is furnished to most communities in the civilized portions of the world, which yields tubercle bacilli in 6 to 10 per cent of the samples examined, the changes necessary to render this supply innocuous are far-reaching. This statement does not take into consideration the possibility that a bovine infection in a human being may often prevent a more serious human infection.

Before taking up a survey of the results of research by many investigators in many countries on the amount of tuberculosis in cattle and the amount of bovine infection in man, let us consider some more or less technical points which must be understood before the conclusions of the different investigators can be given their just value. It is agreed by all bacteriologists who have studied this subject carefully that it is impossible to decide on clinical signs alone whether a case is due to the human or the bovine type of tubercle bacillus. It is true that human pulmonary tuberculosis is almost always due to the human type and that cases of

primary intestinal infection are usually due to the bovine type, if the community is consuming infected milk, but, when contact with both types has been possible, the location of the tissue involved and the progress of the disease suggest only a probability as to the type of the bacillus and are insufficient as proof for settling the question as to the nature of the infection in any given case. For the other forms of clinical tuberculosis we can simply state that the younger the individual is and the greater the probability is of infection by the milk consumed, the more likely is the case to be due to the bovine type.

A vitally important question is the possibility of a bovine strain gradually changing to the human type in the human body. The fact that the bovine type is so much more apt to be found in the human tuberculosis of infancy than in older children and in them than in adults, and also the rather frequent occurrence of atypical strains in certain kinds of tuberculous infection such as lupus, have led a number of prominent investigators, such as von Behring and Calmette, to accept this as a probability. We have carefully studied the problem ourselves and have analyzed the reports of numerous workers on this point, and do not consider that the evidence for the transformation of type is at all convincing. Change of virulence in the body is a possibility, but this is not the only change in the few instances of supposed transformation recorded,—the other characteristics were also changed. There are many difficulties in passage experiments.

The possibility of a latent bovine tuberculosis existing in a calf receiving human bacilli is very difficult to exclude. In some cases the inoculated animals were not even tested with tuberculin, or too long a time elapsed after the test before they were used to exclude a later infection. In other instances the knowledge of the virus inoculated is incomplete; there is even the possibility, in some cases, of a mixed infection. The lack of sufficient controls and of sufficient cultural and virulence tests in rabbits weakens the evidence very markedly. The use of rabbits ought to help one in cases in which contradictory results are found, due apparently to mixed infections. In our own tests the human bacilli retained these characteristics in calves for periods of six months and more.

Apart from the experimental work, which is inconclusive in the few instances in which a transformation was suspected, the persistence of bovine characteristics in bacilli infecting man is very strong evidence against the change of type. In addition to the butcher's tubercle reported, in which instance there was no change in type even after eight years of infection, we have the evidence from typing tuberculous lymph

nodes. The clinical details in many cases give us a reasonable certainty that the lesions have been present over a period of from one to four years or even longer. In one case Oehlecker considers the duration to have been at least six and three-quarter years. Then we have the cases of mixed infection reported by us and others in which the two types are absolutely distinct. These facts, contrasted with the results of passage experiments, in which the ever-present error of spontaneous infection can never be absolutely excluded, should make us careful in drawing any deductions from the small amount of experimental data at hand, which suggest the transformation of the bovine to the human type after a prolonged stay in the human body.

There is therefore no question in the minds of most of those who have done this work on an extensive scale that, while admitting the theoretical possibility of variants developing from characteristic strains, and admitting that they do exist, there is no likelihood of any human lesion due to the tubercle bacillus in which the bacilli show the definite characteristics of the human type ever to have begun in that individual with bacilli having the clear-cut characteristics of the bovine type. We have a right, therefore, to have faith in the determination of the type of the tubercle bacilli in cases of human tuberculosis as at least a fairly accurate index of the total amount of that type of infection in human beings.

The technical details of the determination of the type of the tubercle bacilli are not necessary here. They are widely published in the literature on tuberculosis. There is a general agreement that the difference of vigor of growth on coagulated-egg and glycerin-egg media and of the virulence or lack of virulence of the bacilli in rabbits are sufficient to accurately identify the type of the great majority of the cultures. Practically all cultures growing luxuriantly on glycerin-egg from the start are of the human type, and all cultures growing sparsely or even not at all on glycerin-egg in the first few generations are of the bovine type. It is assumed in such tests that all conditions as to media and temperature are suitable for growth.

In rabbits the bovine type of tubercle bacillus causes a generalized tuberculosis in doses of 0.01 mgm. intravenously, the tuberculosis being progressive and causing the death of the animal. Human viruses injected in the same amount produce no progressive disease at all, or they give rise to lesions of varying severity in the lungs or kidneys or both, and never causing a generalized tuberculosis. Rabbits injected even with the larger dose usually live indefinitely, and, if death should occur, the tuberculous lesions are usually not extensive enough to say that the animal died of the disease.

A milligram dose is not favorable for differentiation. It occasionally produces some generalization in rabbits inoculated with the human virus, whereas with the bovine virus the animal dies so acutely that evident generalization is often not marked. If, however, a rabbit survives the inoculation of 1 milligram, one is sure that the virus is of the human type. Our experience has shown that it is necessary to inoculate from early generations to avoid error due to loss of virulence in occasional cultures.

We have not observed any tendency of the two types to approach each other in rabbit virulence to any extent, which would in any way impair the value of rabbits for differentiation. The attempt should be to use the smallest dose, which, with a bovine virus, almost invariably causes generalized tuberculosis. In this way we should accentuate the difference in virulence so much that slight variations in the human type toward greater virulence will rarely, if ever, lead to any difficulty. If these precautions were taken there are surprisingly few cultures from the usual forms of human tuberculosis whose type cannot be definitely determined.

We are now ready to try to make an estimate of the amount of bovine infection in human beings. Let us first consider its importance in the United States. Combining the figures of Smith, Brown, Lewis and Ravenel we find that, in this earliest work in the United States, all of the eleven cases of pulmonary tuberculosis examined by them were due to the human type, and that of the 21 adults only one was infected with the bovine type and this was a case of cervical tuberculous adenitis. Of 9 cases of cervical tuberculous adenitis in children of from five to sixteen years of age, 7 were due to the bovine bacillus, and of 3 under five years all were due to the bovine bacillus.

In 1910 Krumwiede and I,[2] assisted by a group of workers, made an extensive series of tests in New York City on persons of every age and every kind of case. The results were as shown in table 1.

To get an idea of the extent of infantile infection, the cases obtained from the Babies Hospital are listed in table 2. These cases are representative of New York City children in 1909 and 1910. At this time the general milk supply was not pasteurized, but the majority of infants not nourished by their mothers were fed with boiled or pasteurized milk.

Let us now consider the conditions in England, which are indicated in table 3.

The reports from the German Commission were similar to those from England and America.

[2] Tr. Nat. Assoc. Study and Prev. Tuberc., 6th annual meeting, 1910, 332.

A table of all cases reported in the literature up to 1914 was given by Wang (*Jour. Path. & Bact., 1916, xxi, 131*). This gives probably the most

TABLE 1

Human and bovine bacilli in cases examined, 1910

DIAGNOSIS OF CASES EXAMINED	ADULTS 16 YEARS AND OVER		CHILDREN 5 TO 16 YEARS		CHILDREN UNDER 5 YEARS		NOTES
	Human	Bovine	Human	Bovine	Human	Bovine	
Pulmonary tuberculosis	278		8		5		Clinical diagnosis only known, and therefore no positive details as to extent of tuberculosis elsewhere than in lungs
Tuberculous adenitis, inguinal and axillary	1		4				See next
Tuberculous adenitis, cervical	9		19	8	6	12	In two cases cultures were from axillary node, but primary focus was cervical. Another case died shortly afterward with pulmonary tuberculosis
Abdominal tuberculosis	1		1	1		3	Milk-supply of one child subsequently examined. Tubercle bacilli isolated
Generalized tuberculosis, alimentary origin					1	1	Only two cases are given under this heading. Many of the cases in the following subdivisions showed marked intestinal lesions and some possibly were of alimentary origin
Generalized tuberculosis	2		1		12	4	One bovine case had tuberculous osteomyelitis of metatarsal bone
Generalized tuberculosis, including meninges					18	1	
Tuberculous meningitis			1		14	1	No autopsy. Extent of lesions elsewhere unknown
Tuberculosis of bones and joints	1		10		6		
Genitourinary tuberculosis	3	1	1				The adult bovine case was tuberculosis of one kidney. Removal of kidney. Complete recovery
Tuberculous abscesses	1						Possibly primary in bone
Total	296	1	45	9	62	22	

accurate estimate of the amount of bovine infection existing at that time in Western Europe, the British Isles and the United States (table 4).

TABLE 2

Fatal cases, Babies Hospital, 1910

DIAGNOSIS	CHILDREN 5 TO 16 YEARS		CHILDREN UNDER 5 YEARS		NOTES
	Human	Bovine	Human	Bovine	
Pulmonary tuberculosis			4		One case included probably fatal. Information incomplete
Generalized tuberculosis	1		9	2	
Generalized tuberculosis, including meninges			15	1	One case gave both types of bacilli; included under bovine, as this type caused the meningitis
			See note		
Tuberculous meningitis			11	1	

Total under 5 years, 43, of which 4, or 9 per cent, were due to bovine type

TABLE 3

Compiled from Royal Commission on reports and papers published by Eastwood and F. and A. S. Griffith

VARIETIES	NUMBER OF CASES	PERCENTAGE OF CASES INFECTED WITH BOVINE BACILLI	
		Under 5 years	All ages
Cervical lymph nodes	125	85.0% of 20 cases	48.0%
Lupus	140	66.0% of 50	51.0%
Scrofuloderma	52	58.3% of 12	38.4%
Bone and joint	514	30.2% of 96	19.2%
Genitourinary	21		19.0%
Meningeal	12		16.6%
Pulmonary	275		1.1%
Postmortem cases, children under 12	113	21.3% of 61	All ages under 12 17.6%

These cases in children inder 12 classified according to anatomical distribution of the primary lesion, showing percentage of bovine infections

Alimentary	35		80.0%
Respiratory, double portal (respiratory and alimentary) and uncertain	116		1.8%

TABLE 4

Combined table of all cases (Wang)

CLASSIFICATION	ADULTS, 16 YEARS OR OVER		CHILDREN, 5 TO 16 YEARS		CHILDREN UNDER 5 YEARS	
	Human	Bovine	Human	Bovine	Human	Bovine
Pulmonary tuberculosis, including sputum	1,000	5	28		45	1
Abdominal tuberculosis	24	7	13	17	29	34
Generalized tuberculosis	39	2	32	3	169	22
Genitourinary	35	4	4			
Tuberculous meningitis	6		13	5	55	10
Skin	12	3	4	6	2	
Cervical adenitis	62	10	61	76	18	75
Axillary adenitis	6		8		4	
Bone and joint	82	4	255	61	89	54
Latent tuberculosis	2	1	2	2	4	1
Miscellaneous (other forms)	5	2		1		2
	1,273	38	420	171	415	199
Percentage of bovine infection at each age period	2.9		28.9		32.4	

Total in 2,516 of 16 per cent bovine type

TABLE 5

Proportion of bovine infection in various kinds of human tuberculosis at all ages in England and Wales (Cobbett)

METHOD OF INFECTION	VARIETIES OF TUBERCULOSIS	TYPES OF TUBERCLE BACILLI (PER CENT)	
		Human	Bovine
Group I: Aerial infection	Pulmonary	98.7	1.3*
	Bronchial glands	94.5	5.5
Group II: Food	Intestinal, peritoneal, mesenteric, gland	50	50
	Cervical gland	54	46†
Group III: Various degrees of dissemination from either aerial or food infection	Generalized tuberculosis	84	16
	Meningitis	82	18
	Bones and joints	80	20§
	Genitourinary	82	18
Group IV: Skin infection	Lupus	50	50

* If we take the figures available for the whole world the percentage of bovine infection in pulmonary tuberculosis is only 0.4.

† Mitchell gives 90 per cent for Scottish cases; Griffith, 71.4 per cent for similar cases.

§ Fraser gives 58.6 per cent for Scottish cases; Griffith, 29.6 per cent for similar cases, and in the United States the percentage is 21.6.

During the years of the war, 1914 to 1918, but few bacteriological examinations were made for the type of tubercle bacilli in human cases. Since then the majority of the reports have come from Great Britain and show that the percentage of bovine infection remains high.

Cobbett gave an interesting report in 1922 of the postwar percentage of bovine infection in different types of human tuberculosis (table 5).

It is interesting that Cobbett's figures show that while in England and Wales the bovine type is found in 1.3 per cent of pulmonary tuberculosis, it is only 0.4 per cent for the rest of the countries from which reports have come. These findings will be discussed later under pasteurization. They are clearly due to local conditions: thus, Wang in 1917 reported 11 out of 20 cases of tuberculosis in children tested in Edinburgh as due to the bovine type. In 1915 he tested 406 samples of milk from the same city and found tubercle bacilli in 20 per cent, and Mitchell found the infection in 65 of 72 cases of cervical adenitis to be due to the bovine type. These observers consider this excessive amount of tuberculosis to be due to the large amount of cattle tuberculosis with its consequent milk infection and the common practice of feeding the infants and children in Great Britain on raw milk.

THE DEGREE TO WHICH RAW MILK IS INFECTED BY TUBERCLE BACILLI OF THE BOVINE TYPE

The widespread infection of cattle in Europe and America and the presence of tubercle bacilli in their milk are recognized by all. Early investigations in both regions showed that from 6 to 15 per cent of samples of market milk were infected. Recent investigations have shown that the amount of infection in unheated milk has not declined. England is an example of those countries in which the cattle are very extensively infected.

Brittlebank, Chief Veterinary Officer of Manchester, England, gives a series of figures covering twenty-three years (1901–1923), which show 9.88 per cent of mixed milk samples as found to contain tubercle bacilli, and unfortunately the number sending infected milk in 1923 is greater than in 1901. He estimates that one in three cows is a positive reactor. The bovine population is about 7,500,000 in Great Britain, with 3,000,000 in milk or calf. About 1,000,000 are positive reactors, and are therefore potential producers of infection. Brittlebank states the well-known fact that the main difficulty in freeing herds of tuberculosis is economical. The best milkers and breeders are often those which react earliest.

In 1924 Somer examined 353 samples of Birmingham milk. Twenty-nine of the samples infected guinea pigs with tuberculosis. On the farms producing this milk Somer found 97 suspicious cows. The milk from 31 of these proved to be infected. During the same year in Edinburgh 8.1 per cent of 403 samples were positive. We are now testing 200 samples of the New York City supply, but it is too early to state the outcome.[3] The results of tests in other countries of Europe and America indicate that the cattle are infected everywhere, but in different degrees of from 5 to 30 per cent.

There are two ways in which the danger from bovine tuberculosis to man can be eliminated. The first is comparatively simple and is by heating the milk before it is consumed. This leaves the problem of bovine infection to be handled separately by those interested in animal industry. The second plan is the gradual eradication of tuberculosis from cattle. This is a tremendously difficult and expensive undertaking, but it can be accomplished, at least to a very marked extent. We will consider now the first plan of pasteurization, which should be adopted anyway for the prevention of other diseases than tuberculosis.

There is, I think, a general agreement that the amount and duration of heat found in these and other tests, sufficient to destroy tubercle bacilli in milk, leaves it practically unaltered in taste and nutritive value, with the exception of a moderate loss of certain vitamines. This loss of vitamines is of importance only to infants fed entirely or almost entirely on cow's milk, and can be fully compensated for by the addition of fruit or vegetable juices and, when necessary, codliver oil. Tests on infants have shown that babies fed wholly on pasteurized milk do not gain in weight as well as those on wholesome raw milk, but that the addition of orange juice, and occasionally of codliver oil, makes the pasteurized milk as good as the raw milk.

THE SAFEGUARDING OF HUMAN BEINGS FROM BOVINE INFECTION THROUGH MILK AND BUTTER BY THE PASTEURIZATION OR STERILIZATION OF THESE FOOD PRODUCTS

Among many people of the world it has long been the practice to boil milk before using it for human consumption. This at first was rather for purposes of keeping it in good condition than because of fear of infection.

[3] As this is going to press we have finished the tests. One hundred specimens of raw certified milk showed no infection. One hundred specimens of ordinary milk showed tubercle bacilli in 20 per cent before pasteurization, no bacilli after pasteurization.

Among Western nations the practice of pasteurizing the general milk supply for purposes of preventing infection is growing. In the United States and Canada it is the accepted opinion of most health authorities that the milk supply of communities should be pasteurized before human consumption. This was not only as a protection against tuberculosis, for there seemed to be no other way in which the danger of transmitting through milk the microbes of typhoid fever, septic sore throat, scarlet fever and diphtheria could be prevented. Even where commercial pasteurization of the general milk supply is not done the milk is more and more being heated in the house before it is consumed.

The practical question is how this can be done efficiently and cheaply and with the least possible change in the taste and food value of the milk

TABLE 6

Thermal death-point of tubercle bacilli in milk

TEMPERATURE (FAHRENHEIT)	TIME OF EXPOSURE REQUIRED TO KILL
170°	20 seconds
160°	30 seconds
155°	1 minute
150°	2 minutes
145°	6 minutes
142°	10 minutes
140°	15 minutes
138°	20 minutes
136°	30 minutes
134°	40 minutes
132°	60 minutes

and butter. The degree of heat required to render milk safe is determined by the resistance of the tubercle bacillus, for it is the most resistant of all the bacteria pathogenic to man which are likely to be in it. For the tubercle bacillus, as for all other microörganisms, there is a thermal death-point, which depends not only on the temperature to which it is exposed, but on the duration of the temperature as well. This time for different temperatures was recently again tested by us. Milk, containing tubercle bacilli, was heated by passing it through a pipe surrounded by hot water in such a way that the bacilli were thoroughly exposed. The milk before pasteurizing infected guinea pigs when 1 cc. of 1:10,000 dilution was injected. Table 6 shows results obtained from the inoculations of 1 cc. of the undiluted milk.

Table 6 gives somewhat shorter periods for the various thermal death-

points than those given by a majority of investigators. This was because the bacilli were completely submerged in the milk. Theobald Smith long ago showed that, when the sample of infected milk was heated in a partially submerged flask or test-tube and if there was access to the outside air, the surface of the milk was at a lower temperature than other portions because of the evaporation of the fluid.

When we come to commercial pasteurization we must insist on a somewhat higher temperature and a longer exposure than given in the table, so as to allow a margin of safety, because this cannot be run with the preciseness of a laboratory test. As carried out in this country a commercial pasteurizing plant consists of a heater, in which the milk passes through tubes in contact with hot water and is emptied into a holder. In the holder the milk remains for a minimum of thirty minutes. A heater alone, subjecting the milk to a higher temperature for a shorter time, would suffice if it could be depended upon, but any temporary failure in heating would allow a portion of the milk to pass through without a sufficient destruction of the bacteria. For this reason it is an almost universal regulation in this country for health authorities to still insist on a holder. The temperature of the milk leaving the heater must average about a degree higher than the minimum requirement; for most holders allow of some fall in temperature during the 30 minutes holding of the milk. The majority of communities require that the minimum temperature of every drop of the milk throughout the thirty minutes of holding should not be less than 142° Fahrenheit. This means that the temperature of the milk as it leaves the holder must average at least 142.5° Fahrenheit and more often 144° Fahrenheit, and vary usually between 142.5° Fahrenheit and 145° Fahrenheit. The pasteurizing plants, as a rule, are run efficiently.

Let us look at some results of tests for the type of tubercle bacilli in human cases of tuberculosis investigated before and after the pasteurization of milk was adopted (table 7).

The results of the examinations of the spinal fluid from the cases of tuberculous meningitis revealed, first, that less than 6 per cent were due to bovine bacilli and, second, that the pasteurization of the general milk supply had not made any difference. This was what should have been expected, as children of the age developing meningitis usually received heated milk even at the period of the earlier tests.

The results of the tests in the two periods for the cervical lymph nodes were very striking. The difference between 21 out of 55 due to the bovine type before pasteurization of the general milk supply and 6 out

of 36 after pasteurization is striking enough, but it is more convincing from the further fact that, of the 6, one case certainly developed the infection in prepasteurization days, and that another probably did, and that three of the four remaining cases were fed on raw grade-A milk. On the other hand, of the 30 children who were certainly fed on pasteurized milk, no case of tuberculosis was due to bovine bacilli. Similar results have been obtained from Paris, where unboiled milk is almost never consumed. Thus, in 1917 Burner reported that, in Paris, of infected lymph nodes typed from 19 children none was due to the bovine bacillus.

TABLE 7

Percentage of bovine and human types of tubercle bacilli in tuberculous cervical lymph nodes and in meningitis in New York City before and after the adoption of general pasteurization of the milk supply

1. Before the general pasteurization of milk but after the adoption of the general use of heated milk for infant feeding with the exception of certified milk:

	human	*bovine*	*per cent bovine*
Tuberculous meningitis	54	3	5.3
Tuberculous adenitis (cervical)	34	21	38

2. After pasteurization of the general milk supply but with still the exception of certified milk. This protected raw milk amounted to about 1.5 per cent of the whole supply:

	human	*bovine*	*per cent bovine*
Tuberculous meningitis	48	3*	5.8
Tuberculous adenitis (cervical)	30	6†	16

* There was a history in the case of one of the three, a child two years old, of having been fed on pasteurized milk. In the other two no clear history could be obtained.

† 2 cases: onset of disease in prepasteurization days.
2 cases: grade-A raw milk and certified raw milk.
1 case: fed on ordinary raw milk.
1 case: seven years of age; according to history, was never given cow's milk. Butter might have been the source.

The striking difference between these figures from New York City and Paris, where practically all of the milk is either pasteurized or boiled before being consumed, and in Edinburgh where many infants and very young children consume raw cow's milk, is seen in the figures from Mitchell (table 8), in the *British Medical Journal* in 1914.

Gordon and Brown published in 1923 the results of the examination of 30 tuberculous children from children's and infants' hospital in Boston (table 9). In 1920 Boston already had 90 per cent of its milk supply pasteurized.

Gordon and Brown sum up the results as follows: In a total of 30 cases

of tuberculosis in children under the age of 12 years, the bovine bacillus was identified in 10 instances, or 33⅓ per cent. Twenty-three of the total number of patients were less than 5 years of age. In 6 of these (25 per cent) the bacillus was of the bovine type. The remaining 7 patients were between the ages of 5 and 16 years, and of these there were 4 instances of bovine infection, or 52 per cent. From these figures it can be seen that there was a greater actual incidence of bovine infection in the

TABLE 8

Bovine-type infection in Edinburgh (Mitchell)

Cervical lymph nodes; 1 to 3 years, 25; bovine type 23 Cervical lymph nodes; 3 to 5 years, 17; bovine type 16	93% bovine
Cervical lymph nodes; 5 to 10 years, 25; bovine type 23 Cervical lymph nodes, 10 to 12 years, 10; bovine type 3	74% bovine

TABLE 9

Thirty cases in Boston tabulated according to the method of Park and Krumwiede

CLASSIFICATION	UNDER 5 YEARS		OVER 5 AND UNDER 12 YEARS	
	Human	Bovine	Human	Bovine
Pulmonary tuberculosis	1			
Tuberculous adenitis, cervical		1		1
Generalized tuberculosis, alimentary origin		3		
Generalized tuberculosis	2			
Generalized tuberculosis, including meninges	11	1		
Tuberculous meningitis	3		1	
Tuberculosis of bones and joints			1	2
Genitourinary tuberculosis				1
Tuberculosis of tonsils		1		
Totals	17	6	2	4
Percentage of bovine infection	25		52	

children under 5 years of age, although the number of bovine cases in patients between the ages of 5 and 12 years was relatively greater. Moreover, in the infants under one year of age, the bovine bacillus was identified in only a single instance.

Twenty-two of the total number of cases were known to be fatal. Of these, 4, or 18 per cent, were of the bovine type. Permission for necropsy was obtained in 12 of the fatal cases. Of this number, the cases in which the point of origin of infection was found in the alimentary

tract proved to be, without exception, bovine in type. On the other hand, the human bacillus was recovered from all those cases in which the point of origin, at necropsy, was in the respiratory tract.

In 5 cases out of the total number, the history indicated that the children were exclusively breast-fed. The reliability of this statement on the part of the parents may be regarded as doubtful, for although four of this number showed a human type of infection, the bovine bacillus was recovered in one instance. Since in the latter case (case 8), the patient was 10 months old, it would seem fairly reasonable to assume that, in addition to the breast, there had been supplementary feedings of cow's milk, although this has been denied by the mother. In case 30 there was a very definite and reliable history of the baby's being fed exclusively with "certified" raw milk, since weaning. This history was verified by tracing the source of the infection to the herd which supplied the milk.

From these findings in New York, Paris and Boston there can be no question that the heating of cow's milk and its products is an efficient means of lessening the incidence of bovine infection in man. Not only milk, but milk products, such as butter and cheese, should also be pasteurized.

Winslow and Gray published in 1925 a most comprehensive study of the relation of the number of deaths from pulmonary tuberculosis in cities to the degree of pasteurization enforced. They divided the ciites of the United States into those in which by 1920 only 50 per cent of the milk had been pasteurized and those in which by 1915, 90 per cent or more had been pasteurized. They also grouped separately the cities in which the extent and time of development of pasteurization fell between these two extremes. They contrasted the periods 1911–1915 and 1916–1920. They found that in all cities there had been an improvement in infants under one year of age, but there was no appreciable difference between the improvement in the cities which had delayed pasteurization and those that had adopted it. The same condition was found in pulmonary cases at the age of 1 to 4 years. On the other hand, there was an increase in the death-rate for nonpulmonary tuberculosis between the ages of 1 to 4 years in the cities which had not adopted compulsory pasteurization and a decrease in those that had. The average increase in the death-rate in the first group of cities was 15, while there was a decrease of 18 in the cities that had compulsory pasteurization. An additional point of interest not noted by Winslow is that before the years selected for this

comparison it had become the general practice in all American cities to feed infants under 1 year of age on pasteurized or boiled modified milk, so that the change in a city from a general raw-milk supply to a pasteurized supply would affect chiefly children over one year of age. A somewhat upsetting fact was that the cities which were most tardy in the development of pasteurization had the greatest drop in mortality during the fifteen-year period, leaving out of consideration the city of Denver, to which place a great many cases of tuberculosis go with the hope of benefiting their health. There was no greater number of deaths from adult tuberculosis in the cities not pasteurizing the milk supply then in the cities which did.

THE SUCCESS OF EFFORTS TO ERADICATE TUBERCULOSIS IN CATTLE

Tuberculosis is almost as widespread among cattle as it is among human beings. In our efforts to combat it we have the advantage that we can use any means that we think advisable, without considering the individual rights of the infected cow in the way we must in the case of infected man. Tuberculosis is spread among cattle in their infancy, through their consuming infected milk, and in adult life by contact with infected cows, either directly or through eating food or licking materials contaminated by infected feces or mouth secretions. The same general rules affect cattle as men, in that good housing, fresh air and good food are helpful in preventing the development of serious tuberculosis.

It is upon tuberculin and physical examination that we chiefly depend for the diagnosis of infection, the former for slight infections, the latter for advanced infections. Semiannual tests are necessary; an annual test made by the subcutaneous method, and a semiannual test by the intracutaneous or ophthalmic method or by both. When reactors are found, an intracutaneous test of the rest of the herd should be made at the end of two months. The subcutaneous injection of tuberculin has a tendency to accustom cattle to tuberculin, and if a second injection is made within six months the amount injected should be doubled. Many of the cattle shown by the tuberculin test to be infected are in good general health, and their destruction would be a serious loss to most farmers. As a rule, therefore, the Government steps in and gives the farmer a fair price for the condemned cattle, as estimated by the results of the autopsy findings. So far as I know this attempt has been most extensively carried out in the United States and in some parts of Canada. When a tuberculin test is made, all doubtful reactors, as well as characteristically reacting cattle, should be removed, as among doubtful reactors there will be a fair percentage of tuberculous cattle.

THE SUCCESS OF METHODS USED FOR THE PREVENTION OF TUBERCULOSIS IN CATTLE

Dr. J. A. Kiernan, Chief of the Eradication of Tuberculosis Division, U. S. Bureau of Animal Industry, states that the records of the Bureau of Animal Industry up to very recent times show an increase each year in the incidence of bovine tuberculosis since 1907. Therefore, they instituted in 1917 the eradication programme. The campaign was divided into three projects, namely, (1) the eradication of tuberculosis from purebred herds of cattle (accredited herd plan), (2) the eradication of tuberculosis from circumscribed areas, (3) the eradication of tuberculosis from swine.

The purpose of the Accredited Herd Plan is to safeguard the interests of prospective purchasers of purebred cattle for dairy and breeding purposes by officially accrediting herds found free from tuberculosis. Work has progressed, and is now being carried on in 45 states in coöperation with live stock owners and live stock sanitary officials.

The *Accredited Herd Plan* proposes the elimination of tuberculosis from individual herds, whereas the second project, the eradication from circumscribed areas, contemplates the testing of all herds of cattle within the county, the elimination of the diseased animals, the cleaning and disinfection of the premises and the proper selection of animals from herds known to be healthy to augment the depleted herds from which diseased animals were removed.

The suppression of communicable diseases among meat producing animals is essentially a matter for public health consideration, as well as for the preservation of a healthy animal husbandry. The campaign of controlling tuberculosis whether it be among the people or animals, should be conducted along coöperative lines. Anti-tuberculosis associations, national, state and municipal, can and should assist by various ways in the campaign which is now being conducted throughout the nation in the suppression of tuberculosis among cattle and swine.

At the end of the year 1924, according to the League of Nations International Year Book of 1924, there were in the United States, listed as fully accredited, 48,273 herds, containing 920,370 head of cattle. In addition to the fully accredited herds, 529,018 herds, containing 4,772,826 cattle, had passed one test in the process of becoming accredited. Among 5,312,364 cattle tested in 1924 3.2 per cent were reactors. In 1918, of 134,143 cattle there were 4.9 per cent reactors.

The Bureau of Animal Industry undertook in 1910 to eradicate tuberculosis from cattle in the District of Columbia. In nine years the percentage of cattle infected was reduced from 18.8 per cent to 1 per cent.

The percentage of reduction is about as much as we can hope to achieve and, to retain it, constant care must be continued.

THE EFFECT OF DIFFERENT DEGREES OF CATTLE INFECTION UPON THE AMOUNT OF TUBERCULOSIS IN THE POPULATION CONSUMING THEIR MILK

There is, as already noted, a general agreement that young children are rather readily infected by bovine bacilli. Is there any evidence that such infection increases markedly the death-rate in infants, young children and adults, or does it rather simply substitute a bovine infection in a case which would otherwise probably contract tuberculosis from a human source and, in doing so, either destroy a life or immunize and save it? On the subject we have a very important article by A. Lichtenstein in *Acta Pediatrica*, vol. iii, fasc. 1, 1923. In coöperation with Dr. Arosenius, Under-Secretary of the Statistical Central Office, he compared the percentage of tuberculous cattle in the different sections of Sweden during the years 1911, 1912, 1913 and 1914, with the deaths from human tuberculosis during the same years in the same regions. He considered separately the deaths occurring during the first year, the first five years and at all stages of life. In most of the sections of the country the people rarely changed their homes and their milk supply was from the local dairies. Only in the larger cities was the supply from many sources. These statistics for both cattle and man were carefully gathered and, although certainly not absolutely correct and from a country in which bovine tuberculosis is moderate in amount, nevertheless they are accurate enough to demonstrate whether the prevalence of bovine infection, which varied greatly in different localities, showed any appreciable influence on the total amount of human tuberculosis in infancy or in later periods of life.

The information obtained revealed the fact that the prevalence of tuberculosis in cattle and of fatal tuberculosis in man varies greatly in the different parts of the country, but that there was certainly no evident relation between the amount of cattle tuberculosis and of human tuberculosis. On the other hand, there was a very marked relationship between the mortality from human tuberculosis in infants, in young children and in adults.

Thus, the county of Nobotten, which is situated in the northernmost part of Sweden, has almost no tuberculous cattle, namely, 0.3 per 10,000 as compared with an average of 10 for all of Sweden, and yet it has the

highest mortality of all the counties for human tuberculosis at all ages with the exception of Stockholm and Gottenburg.

Lichtenstein publishes a chart which graphically presents the amount of bovine tuberculosis and of human tuberculosis in the different age-groups in every county of Sweden. As he truly states, "Broadly speaking then, the diagram shows that the death rate due to human tuberculosis displays the corresponding variation in the different counties and that these variations are entirely independent of the frequency of bovine tuberculosis in the different counties." His final conclusion is

> Thus far, Swedish statistics afford no proof whatsoever for the assumption that there is any noteworthy connection between the amount of tuberculosis in either children or adults and of tuberculosis in cattle, but on the contrary, point in the direction that there is a connection between the amount of infantile tuberculosis and the amount of tuberculosis among the population as a whole.

The results of this careful statistical study leave us in some doubt as to the final effect of the moderate number of deaths and the larger number of infections due to the bovine bacillus on the total quantity of human tuberculosis. Some of these deaths and cases would probably have occurred a little later from human infection if the bovine strain had not appeared first, and some of the cases that develped moderate or slight infection from the bovine bacilli might in this way have developed sufficient immunity to give protection from a later infection from the human strain.

These investigations in Sweden should be repeated in other countries. The fact that bovine bacilli are not accountable for more than 10 per cent of the deaths from tuberculosis in childhood and practically none in adults makes it very difficult to prove the importance of bovine infection by vital statistics. As we hope to more and more reduce human tuberculosis it would certainly be unwise to continue to have any more bovine tuberculosis than necessary.

The amount of human infection with tubercle bacilli of the bovine type depends on a number of factors, such as the amount of tuberculosis among cattle, the amount of cow's milk consumed by infants and children, and the degree to which the milk is boiled or pasteurized. The only accurate way to decide that an individual is infected with the bovine bacillus is to isolate the bacillus and test it for its characteristics on culture media and in rabbits. This can only be done by a trained bacteriologist. There is no definite evidence of the transformation in an individual human case of tuberculosis of a bovine into a human strain.

The use of the tuberculin test by the combined use of the subcutaneous, intracutaneous and ophthalmic methods makes it possible to eliminate tuberculosis from a herd and to greatly lessen it in a section of the country. If only individual herds are freed they are likely to become quickly reinfected.

The pasteurization of milk reduces very greatly the amount of bovine infection in a community. If butter is also pasteurized, bovine infection from milk or milk products is practically eliminated. The milk from infected cows should be heated before it is fed to calves. An exposure of the milk to a temperature of 142° to 145°F. for 30 minutes is more than sufficient to kill any tubercle bacilli in it.

While a certain proportion of the tuberculous children of a community have an infection with the bovine type, it is not certain that the total amount of tuberculosis in the community is increased. Those who developed tuberculosis due to the bovine type, and recovered, might have been protected thereby from serious infection with the human type.

Statistics bearing on this question leave this matter in doubt. Notwithstanding this doubt we should attempt to eliminate both bovine and human tuberculosis. The amount of tuberculosis due to the bovine type has decreased more than that due to the human type in cities where pasteurization is in operation.

THE TRANSMISSION OF TUBERCULOSIS THROUGH DOMESTIC ANIMALS

LYDIA RABINOWITSCH-KEMPNER[1]

The thorough investigations made in every country, and more particularly in the United States, during the last 25 years, have proved that animal tuberculosis is closely connected with the tuberculosis of man. As early as 1882 Koch in his classic work on the etiology of tuberculosis pointed out that he knew of no warm-blooded animal entirely immune from infection with the tuberculous virus. In the same work Koch emphasizes that the study of the symptoms produced by tuberculosis in animals of the various species has established the remarkable fact that the course of the disease is different for nearly every animal species. To-day we know that not only is there a great variety of clinical as well as anatomical and pathological changes in the different species of animals, but even in different individuals of the same species tuberculosis may present a very variegated appearance. As to human tuberculosis, noted phthisiotherapeutists are wont to express themselves to the effect that each case of tuberculosis is a case in a class by itself. For some time there prevailed a tendency (especially on the part of the French school) to assume that the variety of symptoms was due to the various degrees of virulence of the infecting bacilli; now, however, besides the differences of virulence of bacilli, the physical condition, temperamental disposition, and immunization of the infected individual and the infected organ are looked upon as decisive factors.

Although there are a great number of references in the earlier literature on tuberculosis to cases of tuberculous infection of human beings through animals, the interrelations existing between human and animal tuberculosis were only cleared up by the numerous investigations inspired by the work of Koch and Theobald Smith.

Tuberculosis is one of the most widely spread of infectious diseases. About one-tenth of all deaths in Germany are caused by it. Thus, during the period, 1920 to 1923, 3,501,561 deaths were reported in Germany, of which 356,472 were caused by tuberculosis. Every 5 minutes

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a human being in Germany dies of tuberculosis. While pulmonary tuberculosis accounts for the greatest number of victims (among the above number there were 301,908 cases of pulmonary tuberculosis and 54,564 of other forms of the disease), the number of deaths from tuberculosis other than pulmonary is nevertheless sufficiently large to call for very serious attention. Besides, it should not be overlooked that, next to mortality, the morbidity also is of importance, and the latter is rather high for tuberculosis of other organs, especially among children.

The above-mentioned investigations, prompted by Smith and Koch, established the fact that there are two different types of the tubercle bacillus, namely, the *typus humanus* and the *typus bovinus*. They differ from each other in both their growth and their pathogenic properties. Both are pathogenic for guinea pigs, but, inoculated in small doses, only the bovine type is pathogenic for rabbits and cattle as well. Besides the *typus humanus* and the *typus bovinus*, the *typus avium*, the bacillus causing avian tuberculosis, is occasionally found in man. The numerous researches in all countries have shown that pulmonary consumption, as far as can be proved by available criteria, is mostly caused by the human type, while in tuberculosis of the lymph nodes and bones (Mitchell reports 90 per cent for Edinburgh), abdominal tuberculosis, miliary tuberculosis and lupus, the bovine type is found very frequently.

It was further established (by Fraser) that the younger the children are, the more frequently can their tuberculous infection be traced to the bovine type. The frequency of infection by the bovine type varies also regionally; thus in England, and more particularly in Scotland, it has been found very often.

From the literature we see that of 1,509 cases of tuberculosis of children (below 16 years) 596, or 26 per cent, and of 1,436 cases among adults, only 81, or 6 per cent, were caused by the bovine bacillus.

When and where, then, is man exposed to infection with bovine tubercle bacilli?

In trying to answer this question, we, of course, think first of all of the domestic animals, that is, of animals useful to man for economic purposes and, therefore, systematically bred by him.

Foremost among these animals are cattle; then follow horses, sheep, goats, donkeys, rabbits, dogs, cats, and the various birds (chickens, pigeons, ducks, geese, parrots, etc.). How, then, do these different animal species behave with respect to tuberculosis? For some time, donkeys, sheep and goats had been supposed to be refractory to tubercu-

lous infection; so were horses supposed to be by some authors. But the above quoted statement of Koch that there are no warm-blooded animals that could escape tuberculosis, when there is opportunity for infection, continues to be correct in every respect.

The compilation of slaughter-house figures (table 1) will best show the actual frequency and distribution of tuberculosis among cattle, calves, pigs and sheep.

Here I would briefly mention that on account of the close relations existing between animals and many people, such as keepers and breeders, knackers, butchers and veterinary surgeons, direct infection is not only easily possible but an established fact. We have descriptions of quite a number of tuberculous skin diseases started by injuries to the skin

TABLE 1

	CATTLE	CALVES	SWINE	SHEEP
1913	247.51	4.37	25.37	1.45
1914	234.08	4.38	22.72	1.20
1915	181.57	3.37	21.24	1.33
1916	190.42	4.25	21.73	1.89
1917	178.10	3.77	18.63	1.98
1918	150.15	4.18	15.76	2.19
1919	169.38	5.87	20.93	2.27
1920	178.65	4.38	20.61	1.69
1921	184.48	3.12	19.97	1.30
1922	183.18	3.20	21.38	1.40
1923	195.87	3.24	20.57	1.84
1924	195.90	3.13	20.17	1.54

which were received in cutting up the tuberculous organs of animals. In a number of these cases tubercle bacilli of the bovine type have been shown to exist in man. In other cases, in which the isolated strain was of the human type, I do not consider it as impossible that the biological properties of the species of microörganism may have undergone a change while the bacilli were in the human body. In this connection I would refer to the joint investigation of this question by Dammann and myself.

More important to man, however, than the above-mentioned danger of infection is the fact that our two most important kinds of food, meat and milk, are provided by cattle.

The danger of infection by eating tuberculous meat is not very great, since the flesh of tuberculous animals is frequently left untainted by the disease. Besides, the flesh of tuberculous animals will not be passed

by the inspectors of butcher's meat, and moreover it is usually exposed to a high degree of heat before it is used for human consumption.

Very great, however, especially for children, is the danger of infection from milk. Examinations of the milk sold on the markets in a great number of different cities have shown that in most cases it contains a greater or smaller percentage of tubercle bacilli. In the milk marketed in Berlin, for instance, live and virulent tubercle bacilli were found in from 14 to 30 per cent of the samples. Further, it appeared that in most cases the tubercle bacilli found were of the bovine type, that is, they originated in the cattle. Now and then, however, tubercle bacilli of the human type were also shown to be present. Thus, Alfred Hess occasionally found bacilli of that type in milk for sale in New York, and I have isolated them from milk on Berlin markets, both in former years and more recently. If the sharp distinction of types is upheld, it must be assumed that these germs originated in man and that the milk was contaminated secondarily with them as a result of lack of cleanliness in handling it. As a rule, however, tuberculous infection of market milk is due to the cows furnishing the milk. Cows with tuberculous udders are especially those furnishing the most virulently infected milk. One cubic centimetre of milk from a cow suffering from tuberculosis of the udder not infrequently contains as many as 100,000 and even one million tubercle bacilli. If such a sample gets into the central dairy gathering, it will, of course, infect all the other milk. But cows suffering from tuberculosis of the udder are not the only ones secreting tubercle bacilli with the milk. Tuberculosis of the udder, in the initial stage, is often enough very hard to diagnose. Most minute changes, discoverable only microscopically, are sufficient to produce a malignant infection. Even when the udder is entirely free from tuberculosis, tubercle bacilli are found in the milk of clinically tuberculous cows. And even the milk of cows showing no clinical symptoms of tuberculosis, but merely reacting to tuberculin, may contain live and virulent tubercle bacilli. My investigations conducted jointly with Kempner, as well as those of Mohler, Adami, Moussu, Gehrmann and Evans, Ravenel, and others, have proved this to be true.

Once the milk has been infected, the tubercle bacilli will pass into the dairy products as well. A great number of investigations have been made regarding this question, both by myself and by others. Furthermore, the germs present in such foods can retain their vitality for a long time (up to 120 days).

Very long experience, I regret to say, has taught me that in many cases even what is marketed as pasteurized milk, supposed to have been freed from germs, does not prove uncontaminated. Besides this, I have often found that the methods employed in pasteurizing milk, while giving satisfactory results in tests made under constant expert supervision, are apt to fail when applied by large wholesale concerns. Nothing but boiling will kill tubercle bacilli under these circumstances, and even in the boiling process attention must be paid to the elimination of any possible sources of failure. One of these sources is the formation of froth. Theobald Smith has shown that germs present in the pellicle and scum of the milk will retain their vitality for quite a long time. Many investigations have been made on the length of heating required to kill the bacilli. Even here results do not agree; but this is easily explained by the variable degree of infection of the milk and the different resistance of the individual species of germ. Ordinary boiling for up to one hour has been stated to be the required time. As to the bad results which come from drinking boiled and especially thoroughly boiled milk, there is no need to comment in the United States, where such extensive researches have been carried on regarding vitamines.

It is a gratifying fact that not every tubercle bacillus entering the body with the food produces tuberculosis. Thus, the maximum quantity of bovine tubercle bacilli remaining harmless to man, even when repeatedly taken in, is estimated by Ostermann at 1,000 in one cubic centimetre. Here too, however, the mere taking in of the bacillus is probably not the only cause producing the disease, but along with it other factors, such as I have mentioned before but which I cannot discuss here in detail, are likely to play an active part.

As early as the middle of the nineties, Siedamgratzky showed that in Germany 1.22 per cent of the slaughtered hogs were infected with tuberculosis. In other countries the percentage was still higher, and seemed to be in direct ratio to the amount of milk given to the hogs. In countries like Denmark, where none but pasteurized milk is used in rearing animals, tuberculosis of hogs has almost completely vanished. It is an interesting fact that tuberculous disease is caused in hogs by each of the three types of the tubercle bacillus, probably in proportion to the respective possibilities of infection by each type. In this connection mention may be made of the English research by Eastwood and Griffith. In the examination of 100 tuberculous hogs, these authors have grown 78 cultures, of which 26 were avian tubercle bacilli, 47 bovine,

1 human, 1 a mixture of avian and bovine, 1 a mixture of bovine and human, and 2 cultures were atypical.

Horses also become diseased with tuberculosis more frequently than had been assumed for some time. The disease seems to occur quite frequently, especially in England. Thus M'Fadyean reported that he had occasion to examine from 12 to 20 cases each year. In the majority of cases the disease was caused by the bovine bacillus, and in a few by the avian bacillus.

As to tuberculosis of sheep, in looking over the literature, we again and again run across reports on individual cases of it. Griffith recently reported two cases, both of which were caused by more or less typical avian tubercle bacilli.

That dogs and cats may get diseased with tuberculosis is a long-established fact. I will here confine myself to a brief report on my own researches in this field. During the time from September, 1920, to April, 1921, I received from Jost of the Berlin Meat Destroying Establishment various organs from 31 dogs and 6 cats, suspected of tuberculosis. In addition to them, I examined 20 normal mesenteric and bronchial lymph nodes taken from dogs, for the purpose of ascertaining whether these too were carriers of tubercle bacilli. They were found to be free from tubercle bacilli, both by microscopic examination and by the characteristics of the cultures grown from them, and in a number of the cases by animal inoculation also.

The canine organs received were, in 24 cases, more or less suspected mesenteric lymph nodes, in 2 of the cases the bronchial lymph nodes also being suspected. In 4 cases the bronchial nodes alone, twice the lung, and once the spleen were suspected.

Of the 6 cats, in 4 cases the mesenteric lymph nodes were infected, being already calcified in two of the cases; once each the lung and the adrenal were diseased.

Of the 19 cultures grown by me from the tuberculous organs taken from dogs, 16 were of the human, and one of the bovine type, while 2 were atypical. Both carriers of the atypical bacilli were among the oldest dogs I received for examination, (terriers, one being from 5 to 6 years, the other about 12 years old).

Of the 6 cats received for examination, 3 were infected with human and 2 with bovine tubercle bacilli. In the sixth case I could not find any trace of tuberculosis.

My investigations in this respect have further shown that the infec-

tion of dogs and cats with tuberculosis, especially in so far as the material of the Berlin Meat Destroying Establishment is concerned, has materially increased since 1914 (with dogs from 1.6 to 2.4 per cent, with cats from 11 to 14.7 per cent).

Titze and Weidanz established the fact, in 1908, that "dogs show a considerable resistance against infection with tubercle bacilli, no matter what method of infection or what type of bacillus is used." By using large doses, however, the authors were able to infect dogs with bacilli of both the human and the bovine types in a great variety of ways. Both types proved equally pathogenic.

Since it is an established fact, therefore, that dogs are not particularly predisposed to tuberculous infection, my positive findings of tuberculosis are even entitled to so much more attention, because they prove that the existing chances of infection must have been ample.

Furthermore, in Berlin during the years preceding my investigations, a great number of dogs were killed. As a result, the material examined by me consisted almost exclusively of young dogs. This is the very reason why the greater part of the dogs examined showed no generalized tuberculosis but only local foci. Since tuberculosis progresses very slowly in dogs, it is safe to assume that the percentage would have been much higher if the examined material had consisted of older dogs.

As was further shown by my investigation, nearly all of the tuberculous dogs examined were of breeds that are the most popular companions of man (ordinary terriers, badger-dogs (*Dachshunde*), wire-haired terriers, etc.).

I cannot close my remarks on domestic animals without discussing the tuberculosis of birds. Among birds living in captivity tuberculosis is a widespread disease; by destroying entire stocks, it may cause enormous losses.

In a very detailed work on tuberculosis of domestic fowls, Eber in 1924 reported that, in the course of his researches and investigations extending over a period of 24 years, he dissected 4,988 fowls, 6.9 per cent of which he found to be infected with tuberculosis. The percentage found by Eber agrees fairly well with the more recent American statistical data. In an examination of about 76,000 chicken-farms distributed over 40 different States of the United States, 4,690, in round figures (6.2 per cent), were found to be infected with tuberculosis.

A series of examinations, which I made, together with Max Koch, a number of years ago, of the large stock of birds in the Zoological Garden at Berlin, showed to me that not only domestic fowls, but all kinds of birds living in captivity, are subject to become diseased with tuberculosis, when there is a chance for infection. Among the 459 birds dissected by us, tuberculous changes were found in 118, or 25.7 per cent. The greatest quota of tuberculous disease was furnished by the perchers (*gallinaceae*), which were followed, in succession according to percentage, by the catchers (*accipitres*), the marsh-birds (*grallae*), the duck-like birds (*lamellirostrals*), the pigeon-like birds (*columbaceous* birds), and the sparrows.

Essentially, avian tuberculosis is an ingestion tuberculosis. The organs especially infected with it are the abdominal organs, the liver and the spleen. As the disease progresses, intestinal tubercles may appear, and these will ulcerate. In such cases large quantities of tubercle bacilli are secreted with the feces, being a very dangerous source of infection.

In my opinion, the bacillus causing tuberculosis in birds does not represent a separate type, but is merely a variety of mammalian tubercle bacilli, adapted to the various animal species.

On the basis of the examination of 95 different species of avian tuberculosis, I was able to set up a complete scale of cultures, from the typical growth of avian tuberculosis, presenting itself in the majority of the cases, up to the characteristic appearance of mammalian-bacillus cultures. Furthermore, from the organs of 3 tuberculous birds cultures of human tubercle bacilli were grown, which had to be classed as such, both on account of their general behavior and from their biological properties. In a single case, the biological habits of a species coming from a parrot and originally designated as avian tuberculosis, were changed by continued passage through animals to such an extent that the culture assumed all the properties of human tubercle bacilli.

The growths showing the characteristics of the avian variety of tubercle bacilli are occasionally found in man as well. Pansini, Kruse, myself, and especially Loewenstein (Vienna) have described such cultures. According to Loewenstein, the infection of man with avian tubercle bacilli often produces characteristic symptoms of disease. It has a tendency of producing a condition of septicemia. Preferred spots are the bone-marrow (medulla) and the kidneys.

SUMMARY

Let me briefly recapitulate what I have said:

1. As a result of the many investigations made during the past 25 years, and inspired by Smith and Koch, 3 different types or 3 different varieties of one species of tubercle bacilli are distinguished, namely, the human type, the bovine type, and the avian type.

2. In *phthisis pulmonum* (pulmonary consumption) of man, mostly bacilli of the human type are found; in abdominal tuberculosis, in tuberculosis of lymph nodes and bones, and especially in human skin diseases, either bovine or atypical tubercle bacilli have been shown to be the cause in many cases.

3. Phthisical (consumptive) people must be looked upon as the principal source of infection with human tuberculosis, their sputum containing numerous tubercle bacilli. While during the past 20 years the prevailing view was that of Flügge and his school, according to which the infection is mainly due to the dissemination of sputum droplets containing tubercle bacilli, of late an ever-increasing number of scientists—I mention only the experiments made by Chaussé and Lange—are raising their voices in favor of the old theory of Cornet that dried tubercle bacilli contained in the dust are the principle source of infection. It is true that it is difficult to tell, in practice, where the infection by droplets ceases and where the infection by dust begins. At the same time, it should not be lost sight of that even infection with bovine tubercle bacilli need not be exclusively due to the consumption of foods containing bovine tubercle bacilli, as was mostly assumed, but, on the contrary, dust will of course contain bacilli of the human type as well as of the bovine and avian types. Now, whenever these germs find a favorable nutrient medium in the infected organ, they will naturally be likely to do their deleterious work. Furthermore, I do not consider it as impossible that the various types, if remaining in the human body for a long time, may occasionally change their biological properties. Among the facts apparently supporting that view are the findings of atypical growths.

4. From all these considerations it follows that not only human tuberculosis, but also that of animals as well, is a danger to man that should not be underestimated. Accordingly, the continued fight against animal tuberculosis is imperatively required, not only in the interest of animal breeding, but for the benefit of human health as well.

5. From the latest reports of the United States Bureau of Animal Industry I see that, thanks to untiring work based on scientific principles and to the large resources at your disposal, you have been able to attain great results in fighting animal tuberculosis. There is no doubt that the restriction of animal tuberculosis will be followed by a decrease of human tuberculosis, especially that of children.

6. So let us not be satisfied, in the continued battle we are waging against tuberculosis, with doing only half the work required, but instead, in considering the sources of infection, let us keep an eye on those as well which, while not appearing very important at first glance, may still work great havoc, if they are overlooked.

STUDIES ON PULMONARY TUBERCULOSIS

II. THE HEALTHY ADULT CHEST

A Clinical and Roentgenological Report

Part I. X-Ray Findings

HENRY K. PANCOAST, F. H. BAETJER AND KENNON DUNHAM

In 1920 the Committee on Medical Research of the National Tuberculosis Association, under a grant from the Association, appointed the following group of clinicians and roentgenologists to establish the X-ray and clinical findings in the chest of the normal or healthy child between the ages of six and ten years:

Dr. H. K. Pancoast and *Dr. H. R. M. Landis*, University of Pennsylvania
Dr. F. H. Baetjer and *Dr. C. R. Austrian*, Johns Hopkins University
Dr. H. K. Dunham and *Dr. K. D. Blackfan*, University of Cincinnati

The report of this X-ray and clinical group was presented before the annual meeting of the National Tuberculosis Association in 1922, and was published in the *Transactions of the National Tuberculosis Association*, as well as in the AMERICAN REVIEW OF TUBERCULOSIS (*1922, vi, 331*). As the work of this group seemed to have produced satisfactory results, the Committee on Medical Research requested the members to continue their studies on the chests of healthy adults, which the members agreed to do. As Dr. Blackfan's interest was in the line of Pediatrics, Dr. Roger S. Morris was nominated to take his place as the clinical associate of Dr. Dunham.

In January, 1923, the members of the group met to determine the policy of their investigations and certain articles of agreement were adopted as a guide to the workings and investigations of the subgroups, substantially as follows:

1. GENERAL PROBLEM

Two age periods were adopted for study; namely, from the ages of approximately 20 to 30 years, and from 45 years on. A period of one and one-half decades was omitted in order to emphasize differences in appearance with advancing years.

2. THE CLINICAL PROBLEM

The clinician of each subgroup was to *personally* examine the individuals selected for the purpose at hand. Only clinically normal or healthy individuals

were to be selected for purposes of study, clinically or roentgenologically, provided any abnormality elsewhere in the body did not in any way affect the chest.

A clinical history was to be made in connection with each individual examined and was to embody the following questions and investigations:

1. Family history, including any history of exposure to respiratory infections to which the individuals selected for study might have been subjected in his family relations.

2. Routine past history of the individual.

3. History of childhood infections, especially measles and whooping cough, and the dates of these.

4. History of any respiratory infections, including influenza, and the dates of these.

5. History of repeated colds.

6. Place of birth and abode of the individual.

7. History of "gassing" if in the army during the war.

8. Each occupation engaged in.

9. Routine Wassermann test if found advisable or necessary.

10. Examine particularly for sinus disease, and either discard positive cases or group them.

3. THE X-RAY PROBLEM

In studying the markings in the lungs, it was decided to attempt to make use both of stereoscopic and flat roentgenograms, for two reasons: first, because it was recognized that each procedure in itself was a sufficient method of study when utilized by an observer trained in the use of it and practised in the procedure of interpretation; and, second, because many examinations of chests must, of necessity, be made by flat films alone, because of grave illness of the patient.

The Base: Relatively circumscribed densities in the lower lobe presenting an appearance of a localized exudate, or density, or suggesting pulmonary exudate, even without giving evidence of any abnormality clinically, were to be excluded from the normal. Individuals presenting definite X-ray evidence of pleural adhesions, partially or totally obliterating the costophrenic angle, and presenting no other definite abnormal appearances in the chest, were to be accepted for normal study, provided they were passed as normal clinically. (The wisdom of this clause was realized by one of the subgroups when, two years later, one of the greatest middle-distance runners of this country was passed over to the roentgenologist as having a healthy chest, and fluoroscopic examination showed the right costophrenic angle completely obliterated by adhesions and the diaphragm very much restricted. This was confirmed by the roentgenograms, which also showed adhesions, but to a less extent, in the left costophrenic angle.)

The Hilum: Calcified lymph nodes at the hilum, without evidences of pulmonary disease, were to be disregarded except as evidences of past infection.

At that time the groups were inclined to regard calcifications as not necessarily tuberculous, but at later meetings they became more of the opinion that these were usually tuberculous in origin. The "inverted comma" was, of itself, to be disregarded. An attempt was to be made to define the extent of the normal hilum shadow on the basis of both stereoscopic and flat-film impressions, especially in relation to the three-zone division of the lung, as described in the report on the normal chest of the child. It was assumed that the density of the hilum shadow would be found such as to permit the preservation of the trunk shadows within it in normally exposed films. In so far as possible, the descriptions employed in the child's chest were to be followed in describing the hilum and trunk shadows in the adult.

The Apical Region: The status of evidence of thickened pleura in the apex, and whether it should be admitted for the purpose of study of the otherwise normal or healthy chest, was left for later decision, as was also the status of thickened trunk-shadows extending to the apical region. A single thickened trunk-shadow extending to the apical periphery, with evidence of a fan-shadow plus localized pleural thickening at the periphery of the fan, was to be regarded as evidence of tuberculosis, past or present. A thickened trunk-shadow with a fan-shadow, without pleural thickening, was also to be so regarded. A thickened trunk-shadow alone was not to be so regarded.

Displacement of the trachea without thyroid enlargement, scoliosis, aneurysm, aortic dilatation, enlarged heart or neoplasm, and with no evidence of any abnormal lung or pleural condition, was not to exclude the individual from selection for study of a normal or healthy chest. All such cases were to be reported, however. Individuals showing slight interlobar pleural thickening without any other abnormality were to be admitted for normal study.

As the work of the subgroups was nearing completion, another meeting was held two years later, in 1925, to determine their policies further and to attempt to agree upon certain additional observations to be made in the interpretations of roentgenograms. As the importance of the field of study was becoming more apparent, consultations were requested, and Dr. William Charles White, Dr. Eugene L. Opie and Dr. Elmer H. Funk were invited to attend.

The subject of calcifications received prolonged discussion, and it was finally agreed, after consultation with Dr. Opie, that calcified spots in the hilum and in the parenchyma of the lungs, without other X-ray evidence of tuberculosis, could be regarded as negative in the absence of any positive clinical evidence of the disease. The group accepted as a fact that such calcifications rarely if ever occurred except as sequellae of tuberculous infections, and that when present elsewhere than the apices probably indicated healed tuberculous foci of childhood.

In view of the many variations found in the X-ray appearance of the adult chest, apparently within normal limits, and the many lasting evidences of

previous disease found in clinically normal chests, it was decided to discontinue the use of the term *normal chest* and adopt that of *healthy chest.*

In order to increase the value of the contribution, it was decided to include in the studies the relations of and variations in all possible extrapulmonary shadows, such as the ribs, the trachea and its bifurcation, the aorta, the heart and the diaphragms. It was further suggested that an attempt be made to determine the divisions of the bronchial tree in relation to the lobes of the lungs, as an aid in determining the location of the lobes and interlobar fissures, and to designate by names in convenient manner all of the more important and constant trunk-shadows.

The final meeting of the groups was held at the Henry Phipps Institute, Philadelphia, May 2, 1926, for the purpose of formulating a final report on the investigations carried out on the healthy adult chest over a period of three years. The following individuals were invited to attend the meeting in consultation, in order that their advice might be sought on various points in the drawing up of conclusions: Drs. William Charles White, Charles J. Hatfield and Paul A. Lewis, representing the Research Committee of the National Tuberculosis Association; Dr. Eugene L. Opie, consultant in pathology; Dr. David R. Lyman, representing the Executive Committee of the National Tuberculosis Association; Dr. Gabriel Tucker, representing Dr. Chevalier Jackson; Dr. F. Maurice McPhedran, roentgenologist of the Henry Phipps Institute; and, because of their close association with the work of the Philadelphia subgroup, Drs. Eugene P. Pendergrass, Kenneth D. A. Allen and DeWitt Kluttz.

Report of the X-Ray Group

The X-ray group has examined 280 individual clinically healthy adult chests as presented to them by the internist members of the Committee. The cases chosen represented for the most part two adult age periods, 18 to 30 years, and from 40 years on, for purposes of comparison. Two hundred of the individuals were examined by stereoscopic roentgenograms and 80 by flat films. One hundred of the former group had lateral roentgenograms made for purposes of study in that view, which is receiving a recognition of increasing importance.

It is not the purpose of the X-ray group to enter into a discussion of technique except to state that all chest roentgenograms intended for pulmonary diagnosis must be of the best possible quality and that stereoscopic films must stereoscope perfectly. There must be as good contact as possible of all parts of the individual's chest with the film or casette-holder. The arms should be thrown away from the side of the chest to

show the axillary folds and the scapulae should be clear of the lung fields. The individual and tube must be symmetrically placed, so that the sternal ends of the clavicles will appear equidistant from the spine. Penetration should be such as to bring out the decreased density of the trachea and the right and left bronchi. When flat films are used, the breast shadow in the female may be confusing, and it may be necessary to make an exposure with the breasts pulled upward and outward, and another with the breasts pulled downward, in order not to obscure a basal lesion or have one suggested that is not present.

The Bones

All of the bones included in the exposures should be carefully noted. Organized pleural exudate at one base is apt to contract the ribs in that locality. Anomalies, such as cervical and bicipital ribs, are likely to be found in between 1 and 2 per cent of cases examined. Calcification of costal cartilages has no bearing, so far as we could determine, upon any pathological condition, and means nothing except that, in a general way, it is more progressive with advancing years, with the following exceptions: calcification of the first cartilage occurs comparatively early, especially in men, and it is very commonly found in the lower cartilages in young thin women. Comparative fixation may play some part in this.

Careful measurements seemed to indicate that in cases of emphysema and in deep-breathers, such as athletes, the ribs are not further apart, but come off from the spine at nearer a right angle and are more nearly horizontal. This is especially demonstrable in the lateral view.

Scoliosis of minor degrees is of no significance in healthy chests, except that one must not misjudge slight displacement of the trachea or other structures because of it.

Soft Parts

Approximate development of fat and musculature can be readily determined from the roentgenograms. By a study of the axillary folds we may be able to judge that the individual is of average nourishment, well-nourished, undernourished, obese, or decidedly underweight. Greatly increased weight, especially in the obese, causes a higher position of the domes of the diaphragm, and this in turn tends to push the heart upward and to the left, both of which tend to obscure the lung bases to a certain extent. The heart may change its position as much as two inches between forced expiration and inspiration in stout individuals.

The Diaphragm

Diaphragmatic excursion was very variable. In athletes and in older adults it was rather uniformly good. Reference has already been made to the middle-distance runner, in whom bilateral adhesions caused very marked diaphragmatic restriction which seemed not in the least to interfere with his athletic prowess. Excursion was rather uniformly poor in thin women.

The X-ray group strongly recommends the use of the term *dome of the diaphragm*, rather than *diaphragm* as descriptive of the curve of the diaphragmatic shadow, as seen in the posteroanterior view.

The right dome was almost always higher by an average of 1.5 cm. in full inspiration. In a few instances both domes were at the same level, and in these individuals the attachment of the inner portion of the right diaphragm was found higher than that of the left. Regular inequalities or waves in a diaphragmatic dome of normal level are due to different levels of attachment, provided inequalities in the upper surface of the liver can be excluded on the right side.

Sharp peaks or tentings of the dome are due to abnormal attachments, such as pleural adhesions, or to changes in the lungs, usually fibrosis. These may be better located and studied to better advantage in the lateral view.

The diaphragms will be considered further in a separate discussion of the lateral view of the chest.

The Heart

The *apex location*, as indicated in the roentgenograms, corresponds closely with the location found clinically, except that in about 50 per cent of cases it was found behind the sixth rib, in the erect posture and during full inspiration, and in the other 50 per cent was more often on a level with the sixth interspace than the fifth (figure 1). The location will vary with the position or size of the individual, and the amount of abdominal fat or distention. At first it was thought that there was considerable difference in the location of the apex clinically and roentgenographically in reference to the midclavicular line, until it was discovered that the location of the clinical midclavicular line and that of the roentgenographic midclavicular line frequently differed considerably. The roentgenologist drops a line directly downward from a point on the clavicle midway between the sternal and acromial ends. Such a mid-

clavicular line does not often run through the middle of the dome of the left diaphragm, especially in thin women, but usually through a point 1 to 2 cm. outside the middle of the dome (figure 1). The heart apex was found within the X-ray midclavicular line in the majority of individuals. It was at or outside this line mostly in older individuals and athletes. This question was discussed at length by the clinical and X-ray members of the group, and the danger of the use of the midclavicular line was recognized as a matter of clinical importance. It was resolved that, from the evidence of roentgenograms, the wide variation in the position of the midclavicular line in its relation to internal structures makes it an unsafe line to use for body measurements. It was recommended, therefore, that in clinical measurements for the apex location and size of the heart, these be measured always from the midline of the body.

It is obvious that accurate cardiac measurements can be made only with the film in front of the patient.

Measurements of the heart-shadow were made in a large number of individuals as a matter of record. Those made were the greatest midline-right and midline-left dimensions and the aortic-shadow width. The anteroposterior dimension was also made in the lateral views. The midline-left and anteroposterior dimensions were found to be greatest in the older men, in whom, also, there was an increase in the average width of the chest. The angle of the heart-axis with the midline was increased most in older men and in the obese.

The heart is further considered under the lateral view of the chest.

The Aorta

The aortic shadow does not extend to the right of the vertebrae normally, but does extend to the left in all instances. The top of the aortic shadow was found to extend to a point varying between the fourth and sixth thoracic vertebrae. In more than two-thirds of the cases examined it was on a level with the body of the fifth vertebra. Apparently there is little or no difference with age, but the height will vary with technique, in that differences in level of the X-ray tube in relation with the patient will alter the vertebral level of the top of the aortic shadow. The lower the tube, the *lower* will be the apparent level of the aorta, because it is nearer the film. The width of the aortic-arch shadow varies somewhat with the size, age and habitus of the individual and the distance of the tube from the film. Estimations of width should be made

with the film in front of the patient. The final decision as to dilatation must be determined by fluoroscopy as well as by the roentgenogram.

The aorta will be considered further under the lateral view of the chest.

The Trachea

As previously stated, all properly exposed roentgenograms should show the decreased density of the trachea, the carina, and the right and left bronchi. It is exceedingly important to be able to detect deviations of the trachea and narrowing of the lumina of the trachea and of the right and left bronchi. With proper technique as to the placing of the individual symmetrically, with the central ray passing through the centre of the body, so that the sternal ends of the clavicle will be equidistant from the spine, and with the neck straight, the trachea in its upper portion will be almost universally in the midline. Any deviations to the right or left above the lower levels of the clavicles are exceedingly slight. In its lower portion the trachea slopes slightly to the right, toward the aorta. Minor degrees of scoliosis will tend to give the impression of lateral deviation. In all cases examined the lumen was found fairly uniform throughout.

A description of the location of the bifurcation of the trachea should be that of the carina. It can be observed only with comparatively high penetration. It was found at levels varying between the body of the fifth and the top of the body of the seventh thoracic vertebrae, and in front of the sixth vertebra in about two-thirds of the individuals examined. It was lower in older persons and higher in women than in men. One of the group thought that the tendency to anteroposterior bowing of the spine might account for the apparent lower position in older persons. The level of the X-ray tube will have some bearing on the relative height of the carina.

The carina was found in the midline, or, more frequently, slightly to the right.

The Bronchi

The top of the right and of the left bronchi crossed the right and left borders of the thoracic spine slightly below the carina level.

The so called *inverted comma* was very frequently found, and usually on the right side. It is a normal appearance, and never represents any

pathological condition. Its tail is the side of the tracheal shadow, and its lower border represents the top of the bronchial wall on that side.

In the lateral view of the chest the right bronchus was always slightly anterior to the left bronchus.

The Hilum Shadow

Although the composition of the hilum shadow is a generally recognized fact, an exact description of the normal hilum and its boundaries presents a very difficult problem. As this shadow is subject to so much change within normal limits and is so very frequently affected by pathological conditions within the chest, it becomes very necessary to define the X-ray hilum in the healthy chest. The anatomical hilum is wholly outside the lung. The X-ray hilum must, of necessity, include a small portion of the root of the lung. The hilum shadow is a conglomerate shadow cast by the bronchi, pulmonary arteries, pulmonary vein, bronchial and some pulmonary lymph nodes, and connective tissue around the root of the lung. It is a hazy shadow, irregular in outline but fairly constant in extent. Its density will vary with the radiographic exposure, and, unfortunately, within normal limits. The trunk-shadows included within its limits should, in normally exposed films, be seen through. If made up, entirely or in part, of a solid mass of homogeneous shadow, the appearance is abnormal.

As there is considerable difference of opinion among roentgenologists as to the exact extent or the anatomical limits of the hilum shadows, it has seemed pertinent to suggest certain boundaries which it is hoped may prove acceptable.

The outer boundary is the most uncertain one. Roughly, it has been regarded as extending to a line limiting the inner zone or third of the lung field. Exact measurements are not possible, inasmuch as they are so variable, and will depend upon the technique. In a number of films measured, the width varied from 5 to 7.5 cm. from the midline, at four feet target-plate distance.

On the right side the normal shadow may be said to extend, from above downward, from the top of the right main bronchus (*B*, figures 3 and 4) to approximately a point where the right lower-lobe bronchus, below the origin of the middle-lobe trunk, begins to subdivide (*I*, figures 3 and 4) into its lower-lobe branches (or trunks) (figure 11). This includes the anatomical hilum, the greater portions of the larger bronchi, and some

lung tissue in front and behind. The extent of this hilum shadow from above downward is approximately two interspaces and a rib.

On the left side the pulmonary artery passes above the left bronchus (*A*, figure 3), and from above downward the left hilum shadow may be said to extend from the upper border of the pulmonary artery down to approximately a point where the left lower-lobe bronchus begins to subdivide (*J*, figure 3) into its lower-lobe branches (or trunks). Such a hilum shadow on this side is slightly shorter than the one on the right and is slightly less than two interspaces and one rib in length.

While the top of the right bronchus is higher than the left, if the tops of the hilum shadows be limited in the manner just described they are on a plane approximately level.

The thickness of the hilum shadow in the anteroposterior direction is a matter that requires further study, and probably largely from the lateral view. Measurements from lateral views are very uncertain and subject to considerable personal equation. One should learn to acquire the idea of depth as well as length and width when interpreting hilum shadows.

The Trunk-Shadows

Extending from the hilum, heavy trunk-shadows pass to each lobe. It has been previously proved that these trunk-shadows represent artery, bronchus and vein. The important point to remember is that each of these trunks contains a bronchus, and that when the trunk-shadows are visible it is possible to map out definitely the location of the various lobes and their bronchi. This can be done readily in stereoscopic roentgenograms, but it is not possible to differentiate the bronchi so well in flat films.

As the structures in the trunks are accompanied by peribronchial and perivascular lymphatics, their shadows may become modified by fibrosis attending old age and following previously existing respiratory-tract infections. As a result, the trunk-shadows are commonly found to be more prominent with advancing years. Careful comparative measurements made at different ages by one member of the group showed that the trunk-shadows did not increase materially in width with age, but presented greater density of shadow, particularly in the presence of emphysema. It was generally agreed that thickening or increased prominence of the trunks to the apices was unusual in the healthy chest, and may or may not be an evidence of disease. Comment on this question has already been made in one of the preceding meeting reports.

Foreign bodies in the air-passages must be located in the bronchus or branch in which they lie. It is very desirable to locate many lesions, such as abscesses, in the lobe or part of the lobe in which they are present, and such localization depends upon a knowledge of the trunk-shadows and their distribution. Differentiation of location in the upper lobe or apex of the lower lobe frequently depends upon stereoscopic location and identification of trunks going to the affected area. For purposes of description, it is very essential that the more important trunks be named and their locations described. There should also be a general agreement as to the names of the bronchi and their relations.

The *right bronchus* or right main bronchus is almost a continuation of the trachea (*T*, figures 3 and 4) except that it bears a little more sharply to the right (*B*, figures 3 and 4). The *right upper-lobe bronchus* is the first subdivision, and comes off from the main bronchus at an angle of about 90° (*C*, figures 3 and 4). Because this branch passes above the right pulmonary artery it is sometimes called the *eparterial bronchus*. The eparterial bronchus shortly divides into other branches: (1) Trunks come off at a sharp angle and pass upward to the apex of the upper lobe, parallel to the spine (*K*, figures 3 and 4). These have been named the *vertebral trunks*, and have an anterior and posterior distribution which can be seen in unusually clear stereoscopic films. This anterior and posterior branching is common to all upper-lobe trunks. (2) *Second-interspace trunks*, coming off behind the level of the second interspace in front, are heavy trunks distributed from behind the second interspace and extending down behind the third interspace. This set of trunks gives off anterior and posterior branches, as is characteristic of all upper-lobe trunks. These branches go to the lower parts of the right upper lobe (*L*, figures 3 and 4). This set of trunks comprises anatomical entities found on careful dissection. They are easily observed.

A third set of trunks may be visualized behind the *first interspace*. This is not an anatomical entity, but made up of branches from the vertebral and second-interspace trunks.

The *right-stem bronchus* is the portion of the right bronchus between the points at which the upper-lobe and the middle-lobe bronchi are given off (*D*, figures 3 and 4). It is very important to designate this area because it is so frequently the point of lodgment of foreign bodies. This is the portion of the right bronchial tree over which the pulmonary artery crosses.

The *right middle-lobe bronchus* (*E*, figures 3 and 4) is given off *an-*

teriorly from the stem-bronchus at a considerable distance below the upper-lobe or eparterial bronchus. This trunk passes in an anterior direction, and appears very short in a flat film. It is seen to good advantage in stereoscopic films only. It has two main branches, one passing down and anteriorly, and the other up and laterally (figure 11). This trunk is important for purposes of localization in posteroanterior views.

The *right lower-lobe bronchus* is a very short portion of the right trunk-system between the middle-lobe bronchus and the bifurcation of trunks to the lower lobe (*F*, figures 3 and 4).

The numerous trunks given off from the lower-lobe bronchus have not been classified. They show great anatomical variations and differ considerably on the two sides. They may become better known through familiarity with iodized-oil injections. In the posteroanterior view they are so numerous and superimposed that identification of individual trunks is almost impossible. Both posteroanterior and lateral views may assist in identification. We could, of course, group them in a general way into mesial or vertebral, posterior, lateral, and apical or superior trunks. The last trunk is an entity and is equally definite on both the right and left sides. It is seen to pass backward from the hilum inside the midscapular line. Its ultimate branches are not generally visualized. Visualization of this trunk identifies the upper third of the lower lobe.

The use of direct intrabronchial injections of iodized oil presents some surprising features in regard to lower-lobe trunk distribution, and especially that to the apex of the lower lobe. Figures 5 and 6 show the height of the apex of this lobe, as indicated by a lipiodol injection in a case of bronchiectasis of the right lower lobe. The lateral view (figure 6) shows how high the apex rises, and the posteroanterior view (figure 5) how much the apex overlaps the upper lobe posteriorly. These illustrations indicate the impossibility of localizing lesions to the upper lobe or the apex of the lower lobe without stereoscopic identification of trunk-shadows in the posteroanterior films, preferably aided by a lateral view. Such localization may not be of so much importance in the case of an early tuberculous lesion, except that it might be mistaken for a hilum density, but it becomes of the utmost importance in the case of abscess or a foreign body. By trunk-shadow and lateral-view localization, primary tuberculous lesions can now be detected in the apex of the lower lobe. Cavities occurring here are frequently called annular shadows.

The *left bronchus* leaves the trachea at a more acute angle than the

right, and passes down under the pulmonary artery and the arch of the aorta by a long sweeping curve (*A*, figures 3 and 4). The left upper-lobe bronchus and trunks to the apex of the upper lobe continue this curve around the arch of the aorta toward the left apex.

The *left upper-lobe bronchus* (*G*, figures 3 and 4), or *hyparterial* bronchus, so called because it passes below the pulmonary artery, is given off a greater distance away from the spine than is the eparterial bronchus.

The trunks come off from the left upper-lobe bronchus, and are distributed in very much the same manner as on the right side, except that there is a trunk (*M*, figures 3 and 4) going to the lingual tip or that part of the left upper lobe which lies over and to the left of the heart. This trunk comes off from the hyparterial bronchus where it breaks up, and extends forward, outward and downward. It is often obscured by the heart shadow. The smaller branches are not seen.

The *left lower-lobe bronchus* (*H*, figures 3 and 4) is longer than the right lower-lobe bronchus but similar in length to the right *stem-bronchus*.

Zones

For convenience of description of the flat film, the lung below the first rib may be divided into three vertical zones, extending outward from the lateral border of the spinal shadow to the lateral chest wall. The inner zone contains the root or hilum shadows. The middle zone contains the trunk-shadows, gradually fading out into their final subdivisions. The peripheral zone contains radiating lines or linear markings from the ultimate trunk-shadows, and gradually fading away in their final divisions before the periphery is quite reached.

Such a division into zones does not apply to stereoscopic films for the reason that the zones cannot be limited by single lines because they extend around the periphery of the entire lung or lobe. Stereoscopically one thinks of these zones more as layers. These are more applicable in connection with the upper lobes, in which the inner zone is occupied by the hilum, the trunk-shadows occupy the middle zone and the linear markings occupy the outer, peripheral or pleural zone, and extend almost but not quite to the periphery or pleura. Roughly, these three zones represent the three thirds of thickness. The linear markings of the vertebral trunks are largely confined to the circle formed by the first rib. Those of the first-interspace trunks are seen mostly behind the first interspace in front and in front of the third and fourth interspaces behind. The linear markings from the second-interspace trunks are visualized

behind the second and third interspaces in front, above the fifth rib laterally and in front of the fifth interspace, and sometimes the sixth, posteriorly.

Calcifications

Calcifications were almost universally noted in one or both hila (figure 1) by two of the three members of the X-ray group, and not so frequently by the third member. Calcifications were occasionally found in the upper lobes, and quite frequently along the heavy trunks to the lower lobes. It must be remembered, however, that pulmonary lymph nodes in the lower lobes extend much further along the subdivisions of the bronchi than in the other lobes, so that calcified nodes here have probably no more significance than in the hilum. This matter seemed so important that Drs. Opie and McPhedran of the Henry Phipps Institute were asked to discuss the matter from the pathological and roentgenological standpoints, as to the significance of calcifications and their proven frequency.

Drs. Opie and McPhedran called attention to the fact that in roentgenograms of children's chests the frequency of calcified nodules within the lungs is usually overestimated. Sharply defined round shadows *suggesting* calcified nodules were found in almost every roentgenogram, but many of these were referable to vascular trunks directed in the axis of the rays. Dr. McPhedran has found that rotation of the patient slightly will cause their disappearance. When these shadows are excluded, calcified lesions of both lungs and lymph nodes may be identified with considerable accuracy. Many are probably missed in the posteroanterior view, being overshadowed by the heart and spine.

They found at the Phipps Institute that calcified tuberculous lesions increased with age, and were more numerous in children of families in which some member suffered with open tuberculosis than in families with no tuberculosis. In children exposed to open tuberculosis there was a gradually progressive increase in recognizable calcified lesions, from 11.1 per cent from birth to 5 years, to 70.6 per cent from 15 years to 20 years. In noncontact cases the figures were 0 per cent and 33.3 per cent respectively.

In children, tracheobronchial lymph nodes with sufficient calcification to make them conspicuous in roentgenograms may be accompanied by progressive tuberculosis. In adults, calcified tracheobronchial lymph nodes are less significant, for in most instances healing has doubtless

occurred. At least two members of the X-ray group were of the opinion that cases showing calcified nodules had developed more resistance to tuberculous infection that those without similar calcification within the lymph nodes at the root of the lung.

Dr. Opie, in a study of excised lungs in 100 children dying from all causes and after roentgenograms had been made, found that calcified lymph nodules in the lungs and hilum were invariably referable to tuberculosis. He has concluded that inflammatory lesions do not cause calcifications in either location. Other forms of calcification are doubtless occasionally encountered, but are so infrequent as to be practically negligible.

The Lateral View of the Chest

As more and more dependence is being placed upon the lateral view of the chest for purposes of diagnosis, one member of the X-ray group made an extended study of this view in collaboration with several colleagues. Most roentgenologists have made lateral-view studies only in the presence of disease, and have not become thoroughly familiar with the normal or healthy chest when viewed in this direction. In fact, their conception of the normal lateral view at this time is comparable to that of the posteroanterior view in the very beginning of their roentgenological work. We feel that this study has been of so much value to us that the imparting of our knowledge cannot fail to be of some value to roentgenologists in general. We strongly urge familiarity with the lateral view of the healthy adult chest as a basis for the recognition of pathological changes. The following striking observations have been made:

1: The *anterior edge of the heart shadow* is in contact with the anterior chest-wall for a variable distance from below upward. The extremes of contact found were from 2 cm. to 11 cm. The average contact was about 7 cm. It was somewhat less in males than in females (figure 7), and least in older males (figures 8 and 10), apparently on account of the bowing forward of the sternum, the bowing of the spine, and the emphysema or increased aeration of the lingual tip of the left lung.

2: The *heart shadow was found to rest below* upon the superimposed diaphragmatic shadows in some part or all of the anterior half of the latter. In over 50 per cent of individuals it rested upon the anterior two-fifths (figures 2 and 7).

3: Attachment of the Pericardium: Extending downward from the

posterior edge of the heart-shadow, from a point where this edge curves forward to rest upon the superimposed diaphragmatic shadows, was found a faint but clearly perceptible shadow, with its posterior border straight or slightly concave, and extending to the superimposed diaphragmatic shadows, or sometimes, visibly to the left diaphragm (figures 7 and 8, and marked by arrows in figures 2 and 10), supposedly attached to the latter at or in front of the middle, and just behind the heart contact point, except in a few instances in which the anteroposterior dimension of the heart was unusually great (figure 8).

This shadow seemed at first to be of some importance because it was interpreted as a backward reflected portion of the pericardial sac passing downward and backward to an attachment to the left diaphragm; and, knowing the posterior curve of the heart-shadow, it was thought that this might be a vantage point for observing slight pericardial effusions or up-and-down movements of the diaphragm in obliterative pericarditis. The possible importance of this shadow led to attempts to identify it accurately, and its exact identification seems advisable lest the shadow be mistaken for some structure it does not represent. The benefit of our investigations will therefore be given.

Anatomists (Gray, Piersol, *et al.*) describe the base of the pericardial sac as firmly attached to the upper surface of the diaphragm throughout its entire extent over the anterior and a portion of the left lobe of the central tendon. Two of the thickened bands of the fibrous pericardium pass downward and backward from the posterior surface of the pericardium on each side of the inferior vena cava to be attached to the diaphragm. These are known as the right and left *phrenopericardial ligaments*. No cavity exists normally between the parietal and visceral layers of the pericardium, except that at the periphery of the base of the sac a slight space exists, and this is occupied normally by a quantity of pericardial fluid.

As a number of pathologists consulted were not familiar with any posterior cul-de-sac of the pericardium at the base, Dr. E. P. Pendergrass and Dr. Max Strumia kindly consented to investigate this region at the autopsy table. They found that, where the lower pericardial sac was attached posteriorly to the left diaphragm, it was reflected backward about 2 cm. posterior to the posteroinferior aspect of the heart, and the posterior wall of the pericardial sac passed downward and backward to meet this posterior diaphragmatic attachment. This formed a cul-de-sac which would readily admit the finger. The cul-de-sac was narrow

laterally; and, when the left diaphragm was pushed down, the posterior edge of the cul-de-sac was made prominent, as in the shadow shown in the lateral roentgenograms. This cul-de-sac was a little to the left of the midline, and will not be found in true midline sagittal sections of anatomical specimens. The structures in this region are well shown in figures 9 and 17 of an article by Fetterolf and Gittings.[1] In the sagittal section, figure 9, the plane of section of the body of a newborn child was 0.75 cm. to the left of the midsternal line.

The supposed pericardial attachment shadow, as shown in the lateral roentgenogram (figures 2, 7, 8, and 10), is too dense to be cast by two thin layers of pericardium alone, even including the phrenopericardial ligaments. It is more dense where uncovered by heart-shadow than is the thoracic aorta lying posterior to it. It is probable that the shadow is a composite one, made up of the inferior vena cava, the phrenopericardial ligaments, and possibly also fluid in the cul-de-sac. It is not likely that the inferior vena cava alone would cast a shadow more dense than that of the descending thoracic aorta. This shadow is practically identical in position, extent and relations in both lateral-right and lateral-left roentgenograms, except that possibly it is a little more dense in the lateral-right views, suggesting that it is made up very largely by the inferior vena cava. It does not disappear on expiration, nor change in general direction in the two phases of respiration, showing that it is not due entirely to reflection of the pericardium put on a stretch. It is much more prominent when the diaphragms descend in full inspiration.

The exact effect, if any, of slight pericardial effusions upon this shadow is unknown. Minor enlargements of the heart pass by or overlap it (figure 8). It is hidden by great enlargements and extensive effusions.

4: The Cardiospinal Space: This is the portion of the retrocardiac space between the posterior border of the heart shadow and the anterior aspect of the shadows of the vertebral bodies. It is always clear normally, except for the faint shadow of the descending thoracic aorta just in front of the spine (figure 10). The usual shape of this space varies from a vertical rectangle (figure 10) to a truncated isosceles (figures 7 and 8) or right-angle triangle (figure 9). It is considerably lessened in width in enlargement of the right or left ventricles or in pericardial effusions. It is increased in width as the anteroposterior diameter of the chest increases in emphysema, or in increased aeration such as is found in athletes (figure 9).

[1] Fetterolf, G., and Gittings, J. C.: Some anatomical features of the child's thorax and their practical application in physical diagnosis, *Am. Jour. Dis. Child., 1911, i, 6.*

5: Relations of the Domes of the Diaphragms: The domes may run parallel from before backward (figure 2) or may cross, in which case the crossing may be about the midline (figure 7), or anterior or posterior (figures 8 and 10) to this point. These relative positions may be altered by a large number of conditions, both normal or abnormal, as, for example, varying degrees of abdominal distention, gas in the fundus of the stomach, a high splenic flexure, pleural adhesions, or hepatic enlargements. The anterior costophrenic sulcus is negligible, but the posterior sulcus is deep. We found the posterior attachment to be 6 to 8 cm. lower than the anterior in thin individuals (figure 2) and about 4 cm. lower in stout persons (figure 9). The extreme differences in level found where 1.5 and 12 cm. On deep inspiration the domes become straighter, but the levels of attachment, of course, remain unchanged. Even with the deep posterior costophrenic sulcus it is not likely that free pleural effusions of any extent could remain undetected here in the anteroposterior view, as they would have to extend laterally to some extent and obliterate the lateral costophrenic sulcus. Small loculated posterior effusions, however, can lie in the posterior sulcus and not be observed in the anteroposterior view.

6: Bronchial Levels: The right bronchus was found invariably anterior to the left. This is the best view to observe deformities, such as stenoses of the trachea and the right and left bronchi.

7: In the chests of older adults showing a tendency toward emphysema (figure 10) and in athletes (figure 9) with unusual lung capacity, the anterosposterior diameter of the chest is decidedly increased and the cardiospinal space is increased. In emphysematous chests the upper portion is further increased in the anteroposterior dimension by forward bowing of the sternum and often by a broad regular kyphosis. The former increases the sternoaortic space (figure 10).

8: The lateral view is a good one by which to note widening of the aorta. In older adults the space between the ascending and descending arches increases (figures 10). This proves that one must be all the more careful to make posteroanterior views without any inclination of the patient, or otherwise the aortic shadow is more likely to be made to appear wider than it should appear. Inspection of a lateral roentgenogram which shows the aortic arch well (figure 10) and comparison with the aortic shadow in a postero-anterior view convince one that it is improper to speak of the *transverse* arch of the aorta. It would certainly be much more accurate to designate this portion as the *horizontal* arch, as suggested to us by Dr. George Fetterolf, because it passes almost directly backward.

FIGURES

Fig. 1. Posteroanterior view of the chest of a healthy, well built adult female (nurse) aged 20

The following points are referred to in the text:

1. A line dropped perpendicularly from the clavicle at a point midway between the sternal and acromial ends passes well outside the middle of the dome of the left diaphragm, and the apex of the heart is well within the roentgenographic midclavicular line.

2. The apex is behind the sixth rib or just below it.

3. Calcifications in the left hilum and left upper lobe are not regarded as pathological.

(*See pp. 434, 435, 442.*)

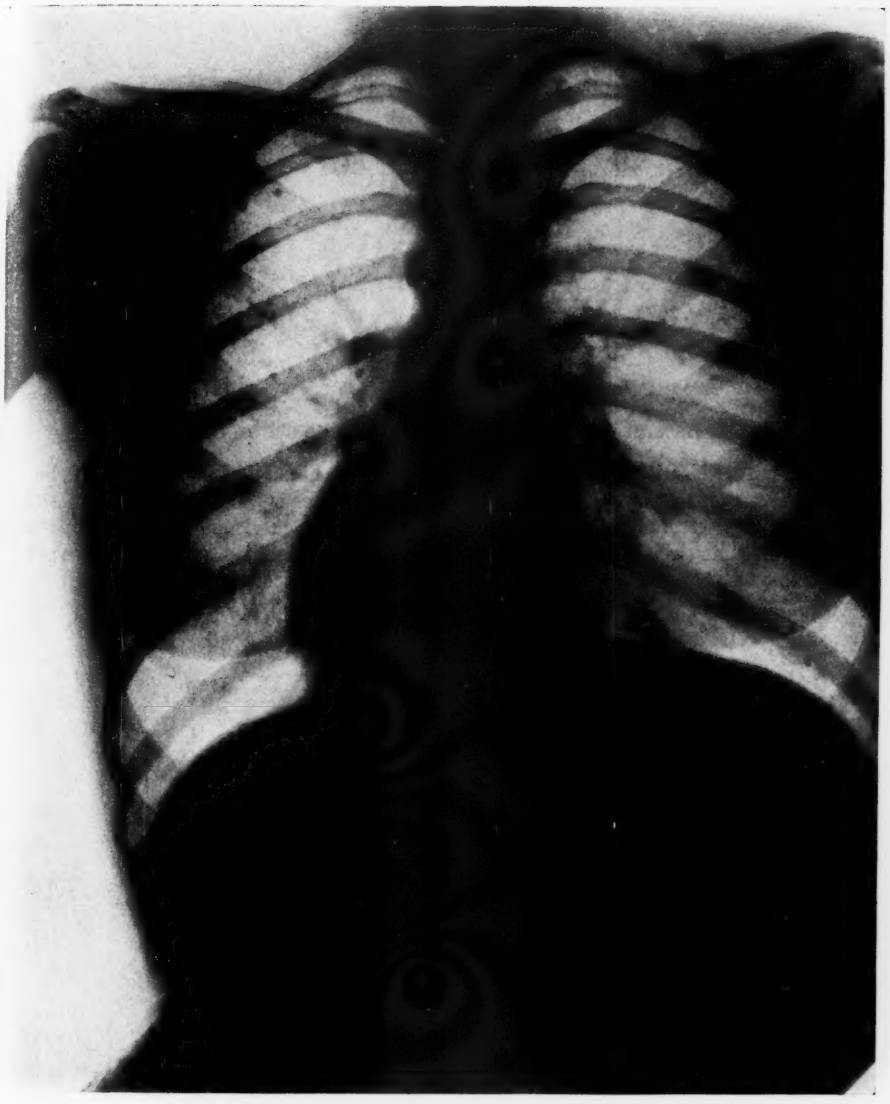

Fig. 2. Lateral view of the same individual as shown in figure 1

The hilum calcifications are seen also in this view. The hilum thickness is indicated, but the two sides overlap and measurements would be difficult or impossible. The composite shadow of the pericardium and inferior vena cava is the slightly curving line, indicated by the arrow, and running vertically to the right of the arrow. The diaphragmatic domes are parallel throughout. Note the much lower level of the posterior costophrenic sulcus.

Fig. 3. Photograph of a white metal cast of the bronchial tree

Loaned to the Committee for study by Dr. Schaeffer of the Jefferson Medical College through Dr. Chevalier Jackson.

T: Trachea.
A: Left bronchus.
B: Right bronchus.
C: Right upper-lobe bronchus.
D: Right stem-bronchus.
E: Right middle bronchus.
F: Right lower-lobe bronchus.
G: Left upper-lobe bronchus.
H: Left lower-lobe bronchus.
I: Point of division of right lower-lobe bronchus into its lower lobe branches.
J: Similar point on left lower-lobe bronchus.
K: Vertebral trunk.
L: Second-interspace trunk.
M: Trunk to the lingual tip of the left upper lobe.
N: Branch of the left lower-lobe bronchus to the apex of the left lower lobe. The corresponding branch on the right side is not shown.

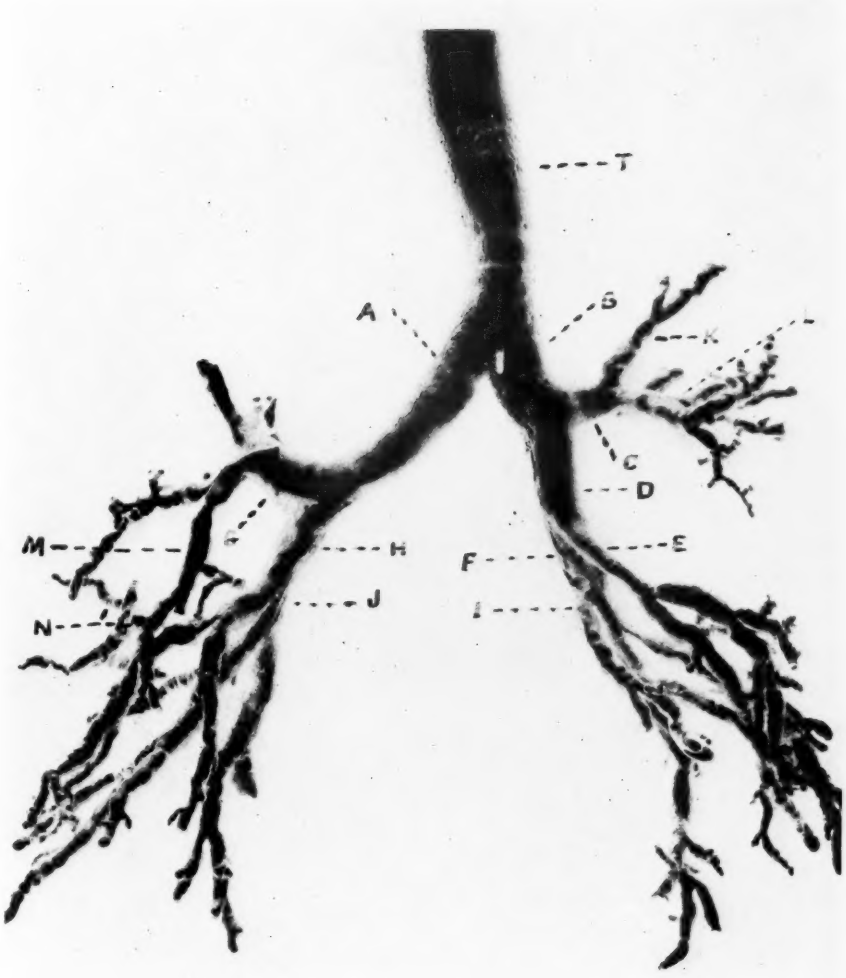
T
A
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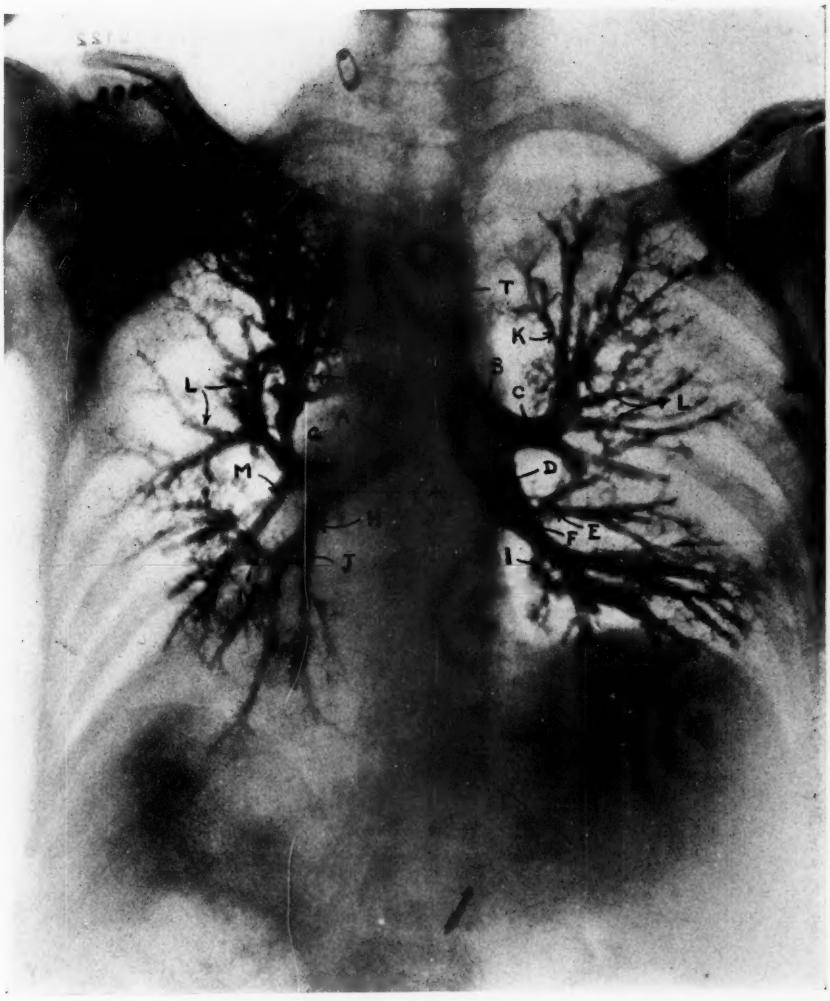
Fig. 4A. Bismuth injection of the lungs in a cadaver immediately after death

Showing the trachea, the right and the left bronchus, and the divisions of the bronchi to all the lobes. The observer can work out from this illustration all of the important trunk-shadows mentioned in this report. There may be some difficulty encountered in applying the right middle-lobe bronchus, *E*, the branch of the left upper-lobe bronchus to the lingual tip, *M*, and that of the lower-lobe bronchus, *N*, to the apex of the lower lobe, to their respective trunk-shadows in stereoscopic roentgenograms. For identification of letters in this illustration, see figure 3.


T
K
B
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L
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D
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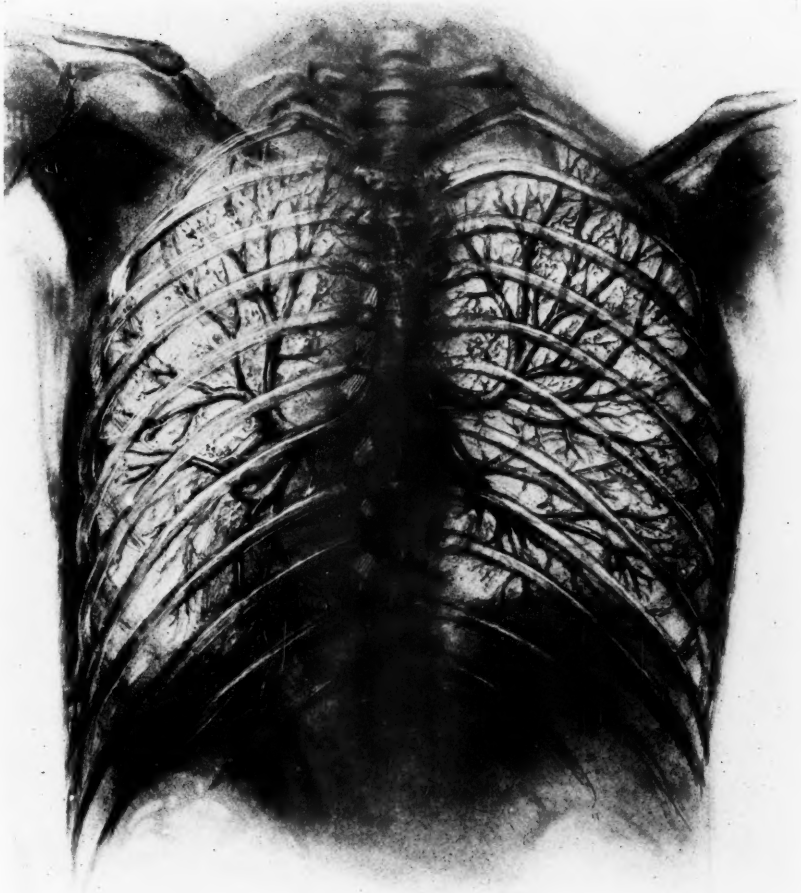
F
E
J
I

Fig. 4B. Composite drawing made essentially from the film represented by figure 4A

Showing the anatomical relations of the trunks to better advantage. For identification of trunk-shadows or bronchial-tree branches see legends of figures 3 and 4A.



Figs. 5 and 6. Lipiodol injection made by Dr. Tucker through bronchoscope directly into the right lower-lobe bronchus

Female, aged 23. The clubbed ends of the branches of the right lower-lobe bronchus indicate bronchiectasis, for the diagnosis and localization of which the injection was made. Note the high level of the apex of the lower lobe as indicated in the higher part of the injection.

Figure 6, a lateral view, shows the extent of the lower lobe and the high level of its apex posteriorly. The bronchiectasis is posterior.

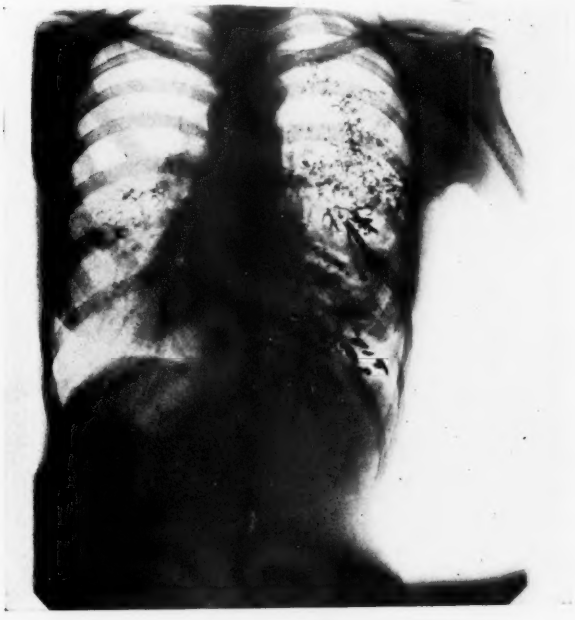


FIG. 5

FIG. 6

Figs. 7, 8 and 9. Lateral views of healthy adult chests

Fig. 7. Healthy adult female (nurse) aged 20. Note the contact of the heart-shadow with that of the anterior chest-wall for a considerable distance and the composite shadow of the pericardium and inferior vena cava. The retrocardiac space is a truncated isosceles triangle in shape. The shadows of the diaphragm domes cross at about the midline or a little posterior to that point.

Fig. 8. Healthy adult male, aged 68. The heart-shadow is in contact with that of the anterior chest-wall for only a comparatively short distance. The composite pericardium and inferior-vena-cava shadow is slightly overlapped by the heart. The retrocardiac space is a truncated isosceles triangle in shape. The diaphragm domes cross well posterior to the midline.

Fig. 9. Healthy adult male (athlete), aged 28. The retrocardiac space is large and a truncated right angle triangle in shape because the anteroposterior diameter of the chest is large and aeration is better than in the average individual. The sternum is not bowed nor the spine bent, as in emphysema. The ribs are more horizontal than in thin chests.

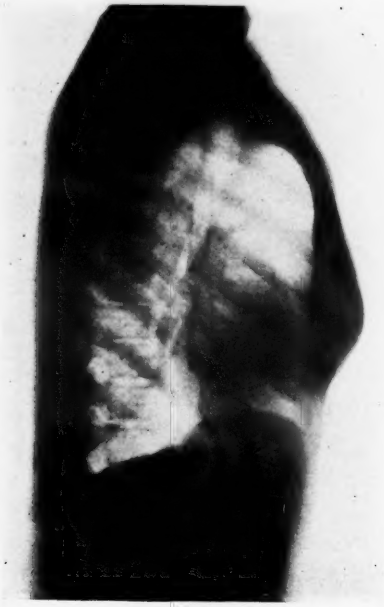


FIG. 7

FIG. 8

FIG. 9

Fig. 10. Lateral view of the chest of adult female, aged 49, and healthy except that she was emphysematous

The retrocardiac space is a vertical rectangle in shape. The diaphragm domes cross posterior to the midline. Because of the emphysema the anteroposterior diameter of the chest is increased, and in the upper portion this is aided by bowing of the sternum and a broad regular kyphosis. The sternoaortic space is increased, and the heart shadow is hardly in contact with the chest-wall. The composite shadow of the pericardial reflection and inferior vena cava, indicated by an arrow, is much more dense than the descending thoracic aorta. The arch shows, probably because of emphysema.

Fig. 11. Bismuth insufflation of right middle-lobe bronchus

It is branching from the stem-bronchus and into its two main branches. The patient was examined for Dr. Gabriel Tucker. The top of the right bronchus is faintly outlined, as are also the lower-lobe bronchus and its branches, and the proposed upper and lower limits of the hilum shadow are thus indicated.

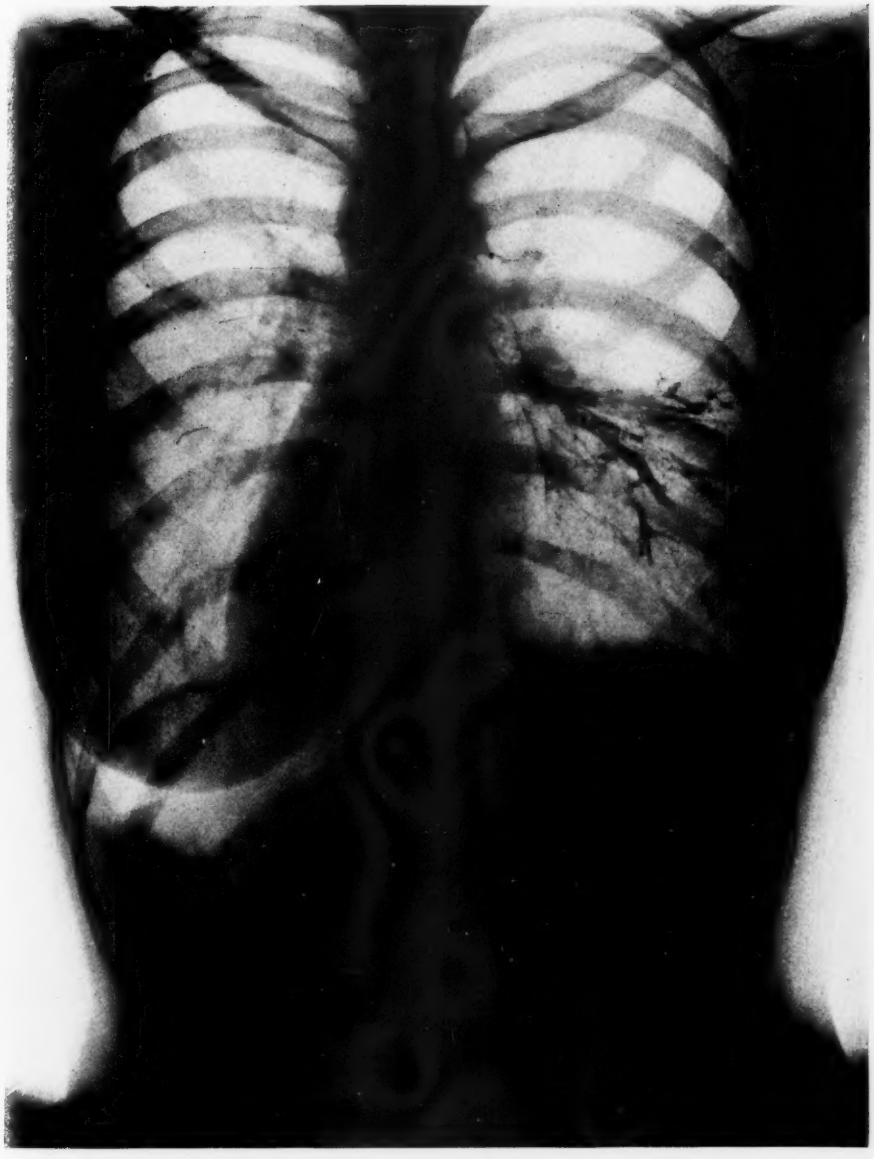


Fig. 12. Lateral view of the chest of a male, aged 63

There is a supposed tumor in the right upper lobe indicated by the rounded denser shadow, while the remaining portion of the lobe is clouded by atelectasis due to obstruction in the upper-lobe bronchus (*A*, figure 14). Below the upper lobe, in front, is the less dense middle-lobe, shown throughout its greatest extent, with the apex approximately at the point indicated by the arrow. The fissure between the upper and lower lobes, posteriorly, and the middle and lower lobes, anteriorly, is indicated by pleural exudate. While this does not indicate a normal or healthy chest, the pathological features distort but little, and the illustration shows the location of the three lobes in the lateral view probably better than they could be shown in any other way during life. Later studies of this case showed a cavity in the supposed tumor shadows, and the diagnosis was changed to abscess, which was confirmed at operation.

Fig. 13. The same case as in figure 12 after lipiodol injection into the right bronchus

This shows the distribution of the middle-lobe bronchus, *B*, and its branches, and that of the lower-lobe bronchus and its branches. The branch to the upper portion of the lower lobe, coming off at *C*, does not have its upper divisions filled.

Fig. 14. Posteroanterior view of the same case as in figures 12 and 13

Showing the obstructed upper-lobe bronchus, *A*, the right middle-lobe bronchus coming off at *B*, and the lower-lobe bronchus dividing at *C*. The shadows of the middle and the lower-lobe bronchus divisions overlap in the flat film. The abscess shadow has been partially blocked out in the reproduction in order to show the bronchi. The lipiodol injection was made by Dr. Gabriel Tucker.

R

INTRATHORACIC ANNULAR SHADOWS[1]

R. S. E. MURRAY[2]

Recent medical literature on the X-ray findings in pulmonary tuberculosis contains a number of discussions concerning the true nature of the so called "annular shadow" (see appended bibliography). To briefly describe these forms, they are characterized by a ring-like shape, which is sometimes a perfect circle. Other shapes are encountered, such as elliptical, oblong, square, dumb-bell, and combinations of these. The outline may be quite thin and altogether lacking in adjacent infiltration, or the shadow-wall may be very thick and surrounded by dense infiltration. These shadows may persist over long periods of time, undergoing little or no change. On the other hand, we have observed annular shadows come and go in a few months or even weeks. Theoretically, this peculiar configuration may be caused by a circumscribed tissue-loss, occurring in the parenchymatous mass of the lung, or less frequently by a localized adenolymphatic dissolution within the confines of the central hilum, or it may be produced by isolated areas of spontaneous pneumothorax, developed in the interlobar septa or between the peripheral layers of the pleura. It is readily admitted that the importance of differentiating between cavity-formation and localized pneumothorax seriously concerns the prognosis and treatment in each individual case, not to mention the prestige of the roentgenologist. Consequently, it is demanded that the roentgenologist interpret the meaning of these ring-like shadows with a degree of accuracy which will not admit of doubt. With our present electrical, chemical and optical armamentarium this position is attainable. The roentgenologist can and should be emphatic in presuming to explain the exact nature of these shadows.

In regard to technique, over a period of three years, involving an exposure of more than 11,000 patients, we have experimented with target-plate distances varying from 60 to 200 cm., with milliamperages ranging from 20 to 120, with and without intensifying screens. The finest and

[1] Publication authorized by the President of the Board of Managers, National Home for Disabled Soldiers, Dayton, Ohio.

[2] Roentgenologist, National Sanatorium, Tennessee.

clearest films have been obtained using a target-plate distance of 75 cm., a milliamperage of 85, a kilovoltage of 85 (equivalent to about 15 cm. point spark gap), a 100 milliampere *Universal-Radiator* Coolidge tube, intensifying screens, and a time averaging 0.2 second. Great care is exercised in explaining the procedure to the patients. The word of command is precise and snappy, thus: "Take a nice easy breath. Hold it steady. Don't breathe." As all plate-changing and tube-shifting are done electromagnetically, the whole operation involving the taking of a stereoscopic pair does not occupy more than one second. The dark-room is absolutely light-tight, and all chemicals are fresh and held at the proper temperature. A special Wheatstone stereoscope, having several meritorious innovations, is used in the study of the films. The mechanical and optical details of this piece of apparatus are designed to angulate, coördinate, illuminate and magnify the film pictures, so that stereoscopy, brilliance of transillumination and magnification of detail are combined to produce the least possible eye-strain with prolonged periods of observation.

With the above exposure and viewing technique, the delineation of lung tissue becomes extraordinarily detailed and clear cut. The size, shape and position of annular shadows can be determined with great accuracy. Occasional exceptions are encountered, when the particular shadow which commands our attention is more or less hidden by surrounding parenchymatous density or greatly thickened pleura. Reëxamination with suitably increased exposure-time will clarify this situation. In studying a particular shadow the first observation to be made is the actual detail of its contour. Small channels, which may connect it with the central hilum shadow, must be diligently searched for. These drainage channels constitute the crux of the evaluation of annular shadows. All annular shadows which are due to cavitation show these drainage channels. Sometimes the pathway to the outer respiratory passages is devious and partly obscured by other shadows expressing pathological changes; but if the annular shadow is due to cavity, the drainage channel is there, and can be identified as such. A true cavity in the parenchymatous area of the lung cannot exist as an isolated entity. This is quite possible in tuberculous nephritis, but not in tuberculous affections of the lung. Annular shadows, caused by small localized areas of pleural separation constituting pneumothoraces, do not subtend drainage channels, unless connected up with adjacent cavity formation, which is associated with an empyema, due to infection of the pleural cavity. The second observation to be made is the relation of the shadow to other

structures in proximity. A deeply seated annular shadow at or about the centre of the lobe of a lung cannot be due to pneumothorax. On the other hand, should such a shadow lie out in the periphery of the lung and show the drainage channel, the interpretation is cavity. The third observation of value lies in the detail of the shadow itself. In a number of cases it has been found that those presenting annular shadows—cavities—with very thin walls are more liable to repeated hemorrhage than those with thick fibrous-walled cavities.

In regard to the matter of incidence, 47 per cent of all our cases, which have been definitely active for a year or more, have shown annular shadows. Of the shadows themselves, 80 per cent are definitely due to cavitation.

This whole matter of the evaluation of annular shadows, summed up simply, amounts to this: With our present precision apparatus for exposing and viewing, the roentgenologist is in a position to produce films, which actually contain the desired information; and precision stereoscopic magnification of the shadow detail certainly tends to resolve the intricate pencillings into actual structural forms.

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ARTIFICIAL PNEUMOTHORAX FOLLOWING SPONTANEOUS PNEUMOTHORAX OF CONTRALATERAL LUNG[1]

HERBERT F. GAMMONS

The following case is reported because in many features it is unique.

E. N. G., male, age 24, was admitted March 23, 1926. Previous history unimportant. Physical examination showed medium, coarse, posttussive râles above 5th rib to apex, and to 7th dorsal spine on right side, with marked friction sound at left base, anteriorly and laterally. Blood examination was positive for malaria. Sputum contained tubercle bacilli. Urine negative and Moro cutaneous test positive. Examination was negative otherwise except for chronic left otitis media. Temperature elevated, averaging 101°F., and cough very troublesome. On April 28, complete left-sided spontaneous pneumothorax developed, and temperature rose to 106°F. and pulse to 140. This temperature continued for three days with slight remissions. On April 29, 500 cc. of air was removed from left pleural cavity, with improvement in respiration and decrease of pressure. On May 7, 1500 cc. of air removed. Fluid formed in left pleural cavity; and, July 3, 500 cc. of straw-colored fluid aspirated, and this followed by relief of labored respiration. Physical examination showed partly expanded left lung, with fluid at base. Right lung showed râles throughout, with cavitation in upper lobe. Cough was becoming very troublesome, and copious hemorrhages occurred, apparently from right lung at top. Artificial pneumothorax was considered for relief of cough and hemorrhage, and, after advising patient of possibilities of recurrence of rupture of left lung and after obtaining his consent for operation, 500 cc. of air was instilled into right pleural cavity, August 18. There was positive pressure at beginning of operation, and this was more positive after treatment. August 20, 600 cc. given; August 27, 400 cc.; August 30, 450 cc.; September 2, 500 cc.; September 9, 400 cc.; September 13, 400 cc.; and September 20, 400 cc. There was always positive pressure before treatment. Moro test negative before inducing pneumothorax, and remained so. On admission it was positive.

The hemorrhages ceased; cough, expectoration and fever improved; and physical examination showed an apical collapse with obliteration of cavity

[1]From the Arkansas Tuberculosis Sanatorium, Booneville, Arkansas, Dr. John Stewart, Superintendent.

in right side and a fairly well-functioning lung on left side. There was slight dyspnea after the first treatment but none after the others.

The patient developed pain in the left ear. The ear-drum was inflamed but not bulging. A few days later the ear-drum burst and there was a small amount of discharge.

The patient was worried about the ear condition and left the institution to seek a specialist's care for it.

While the prognosis in this case is unfavorable the case is of interest for the following reasons:

1. The spontaneous pneumothorax in the good lung was probably due to traction of pleural adhesions at the base during cough.
2. Deflation and aspiration relieved the symptoms.
3. It was possible to induce pneumothorax on the side opposite to the spontaneous pneumothorax.
4. An apical collapse resulted on the induced-pneumothorax side, with relief of hemorrhage, cough and expectoration.

THE MOTOR, SENSORY AND TROPHIC REFLEXES FROM THE LUNG

AND THE NERVE PATHS THROUGH WHICH THEY ARE EXPRESSED

F. M. POTTENGER

PULMONARY REFLEXES SHOWN IN SKELETAL TISSUES

I first noticed an increased tension in the pectoralis muscle on the side in which the lesion was found in a patient suffering from pulmonary tuberculosis in October, 1908. The first description of this was published in March, 1909 (1). At first the fact was somewhat bewildering and I made errors in my explanations (2), in not differentiating the reflex paths from the lung from those from the pleura. This was due to the fact that the path or paths through which such a reflex could take place had not yet been described by physiologists.

When I had satisfied myself beyond doubt that this was a pulmonary motor reflex and that it was constantly present on the side showing activity in the lung, I began to seek for an explanation. With increased experience in its detection I was able to assure myself that the motor reflex from the lung, as it affects the voluntary muscles, was expressed in not only the pectoralis but in all muscles which receive their innervation from the central cervical segments of the cord, particularly the IIId, IVth and Vth, as shown in figure 1, and that it is much less evident in the pectoralis than in others, particularly the sternocleidomastoideus, scaleni, trapezius, levator anguli scapulae, rhomboidei, and central tendon of the diaphragm (3). It is a particularly important fact that the intercostal muscles do not show the pulmonary motor reflex.

Observation convinced me that this motor reflex was an expression of activity and that, after the disease had become chronic or after it had healed, the motor reflex became less evident and finally disappeared, atrophy of the muscles taking the place of the previous spasm (4). In other words, the muscles became atrophied from injury to the neurons caused by the prolonged irritation due to the chronic character of the inflammation; and after the acute stimulation had ceased, the trophic effects alone remained.

Sensory changes previously had been described as affecting certain cervical cutaneous zones (5). In order to understand the sensory reflex from any organ one must know that there are many forms of sensory expression. The sensory reflex is not always a pain. It may be a dull sensation, an aching, a soreness, a feeling of oppression, or changes in perception of heat and cold. The sensory changes from the lung are rarely those of acute pain, but usually those of the deep and protopathic types as described by Head (6). They may be expressed in all deep tis-

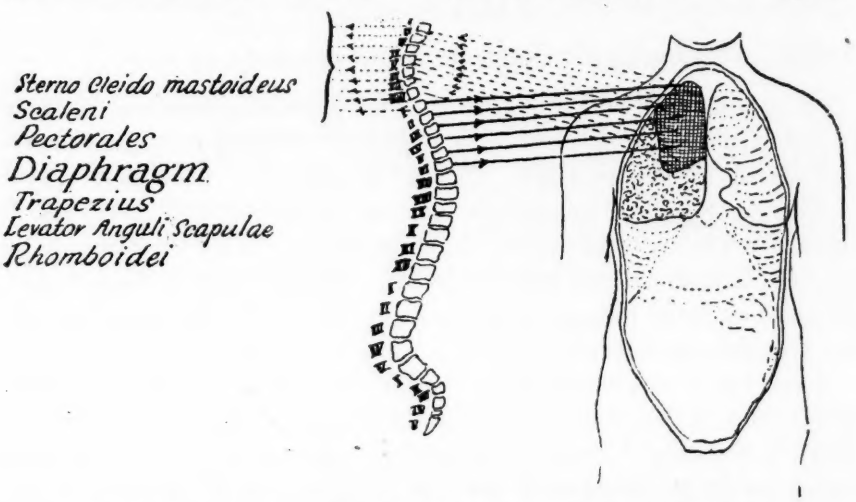

FIG. 1. SCHEMATIC ILLUSTRATION OF PULMONARY VISCEROMOTOR REFLEX

Lines running between the lung and the spinal cord represent sympathetic nerves. Solid lines carry innervation to the lung. Broken lines carry the impulses from the lung to the cord, where they are transmitted in the cervical portion to the spinal motor nerves, which complete the reflex. The muscles involved in this reflex are shown in the illustration. The path of the reflex is not, as shown in the illustration, directly from the lung to the cervical portion of the cord, but back to the upper six thoracic segments, from which it is carried upward to the cervical portion of the cord by intercalated neurons.

sues supplied by sensory nerves which arise from the same cervical segments of the cord as the motor nerves which express the motor reflex from the lung. A sharper pain is occasionally found in the skin, in Head's sensory zones, which take their innervation from the midcervical portion of the cord; but this is rare.

The trophic reflex expresses itself in all the tissues that show sensory and motor reflexes from the lung; consequently it is found in all muscles shown in figure 1 and the skin and subcutaneous tissue in the cervical segments III, IV and V, as shown in figures 2A and 2B.

When we were definitely able to recognize these three types of reflexes, (1) motor, (2) trophic and (3) sensory, originating in the lung and expressing themselves in the skeletal structures supplied by nerves from the midcervical segments of the cord, our next step was to determine the

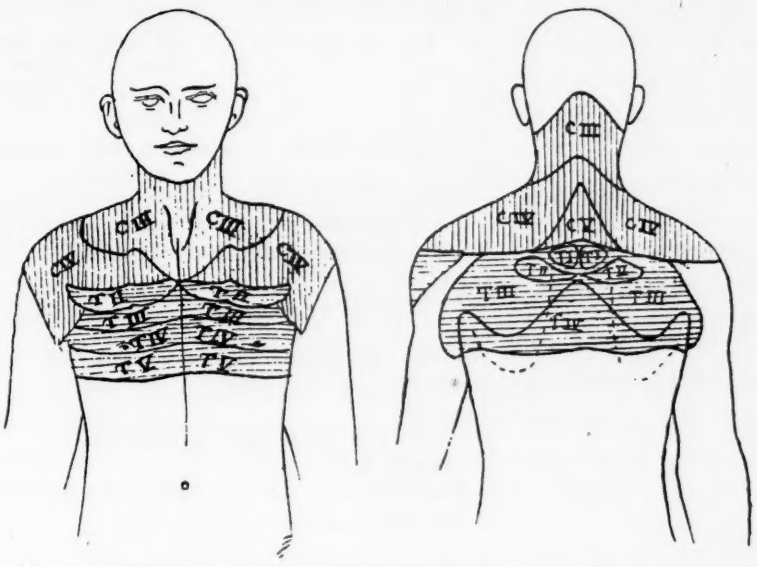

FIG. 2A FIG. 2B

FIG. 2A. SHOWING THE CUTANEOUS AND SUBCUTANEOUS AREAS WHICH ARE AFFECTED BY THE PULMONARY VISCEROSENSORY AND VISCEROTROPHIC REFLEXES. ANTERIOR VIEW

This viscerotrophic reflex is shown particularly as a degeneration of the skin and subcutaneous tissue supplied by the IIId and IVth, and slightly by the Vth, cervical sensory roots. It will be seen that anteriorly this includes the tissues of the neck, shoulders and chest down as far as the second rib.

FIG. 2B. SHOWING THE CUTANEOUS AND SUBCUTANEOUS AREAS WHICH ARE AFFECTED BY THE PULMONARY VISCEROSENSORY AND VISCEROTROPHIC REFLEXES. POSTERIOR VIEW

This includes the neck, shoulders, and that portion of the chest above the spine of the scapula. The interscapular tissues involving T. I, T. II, T. III, and T. IV show the "hilum saucer of degeneration."

afferent paths. In order to obtain this information I was led deeply into the study of visceral neurology. It was necessary to understand the vegetative nervous system and its relationship to the voluntary nervous system, the laws governing reflexes, factors which influence physio-

TABLE 1

REFLEX SYMPTOMS FROM THE LUNG

Afferent Nerves		*Symptoms*	*Efferent Nerves*
INFLAMMATION OF LUNG		Hoarseness	Laryngeal nerves
		Laryngeal irritation	Superior laryngeal nerve
		Cough	Laryngeal and nerves to all expiratory muscles with inhibition of nerves to inspiratory muscles
		Inhibition of heart	Motor fibres of cardiac vagus
	Afferent through (vagus) parasympathetics	Increased muscle tonus and glandular secretion in gastrointestinal canal	Motor fibres of gastric and intestinal parasympathetic
		Flushing of face	Sensory fibres of trigeminus
		Spasm of sternocleidomastoideus and trapezius	Spinal accessorius
		Deviation of tongue from median line	Hypoglossus
		Degeneration of facial muscles	Trigeminus and facialis
		Flushing of ear	Third sensory cervical
		Dilation of pupil	Motor from Budge's Centre (lower cervical and upper dorsal)
		Spasm of muscles of shoulder girdle and diaphragm	Cervical motor nerves, IId to VIIIth
		Lessened motion of chest-wall, partly due to muscle spasm as above	Cervical motor nerves, IId to VIIIth
	Afferent through sympathetics	Pain above 2d rib and spine of scapula (superficial)	Cervical sensory nerves, particularly IIId, IVth and Vth
		Pain in muscles of shoulder girdle (deep pain)	Cervical sensory nerves, IId to VIIIth
		Degeneration of skin and subcutaneous tissue above 2d rib anteriorly and spine of scapula	Cervical sensory nerves, IIId, IVth and Vth
		Degeneration of muscles of shoulder girdle	Cervical sensory and motor, IId to VIIIth

logical action, and embryology with its developmental and segmental relationships.

There are numerous reflexes possible from the stimulation of any organ or tissue. One must always bear in mind the integrative function of the nervous system if the proper conception of physiological action is to be had. The action of the various tissues of the body are brought into one complete whole by the nervous system. A stimulus entering one segment of the cord may be transmitted to other segments far removed from it before it causes action. For example, inflammation of the bladder will at times produce spasm of the gastric pylorus or cardia. Pain anywhere in the body may produce dilatation of the pupil. The impulses travel over many segments of the cord in order to produce such action.

Table 1 shows some of the common reflexes which arise from the lung. I have classified them according to the afferent path followed as vagus or parasympathetic reflexes and sympathetic reflexes. I have also shown the efferent nerves through which the reflexes are completed.

One of the difficulties which I early encountered was to differentiate pulmonary from pleural reflexes, but I soon found that the pleural reflexes which are mediated through the sympathetics and intercostals with spinal nerves are expressed most regularly over the bony thorax and immediately over the area of involvement. This is true not only of the motor but also of the sensory and trophic reflexes. Only occasionally, when the lower costal pleura and the costal portion of the diaphragmatic pleura are involved, will the reflexes extend to adjacent tissues down over the abdomen (7). Pleural trophic and sensory reflexes, which are mediated through the phrenics, are expressed in the midcervical segments of the cord. I also realize that sympathetic pleural reflexes might occur through the same midcervical spinal nerves that show pulmonary reflexes because the visceral pleura is supplied by the same sympathetic nerves as the underlying lung; yet I have never been able to identify a motor reflex in the muscles of the neck as a result of acute pleural inflammation, nor a trophic reflex in this area as being unquestionably of pleural origin.

NERVE SUPPLY OF LUNG

Both sympathetic and parasympathetic fibres enter the lung at the hilum and follow the bronchi throughout the organ (Müller (8)). The parasympathetics are represented by the vagus and the sympathetics by the fibres taking their origin from the upper five or six thoracic segments of the cord.

It is the particular function of the vagus of the parasympathetic system, when stimulated, to activate the bronchial musculature and the glands of the bronchial mucous membrane. It is the particular function of the sympathetics to oppose the vagus in its action, thus to relax the bronchial musculature and decrease bronchial secretion. The sympathetics also control the action of the blood vessels.

In discussing the innervation of the lungs and the antagonism between the vagus and the sympathetics, Gaskell (9) says:

> In other cases of endodermal musculature we find indications of the reciprocal innervation between the enteral (parasympathetic) and sympathetic systems; thus the motor cells of the endodermal musculature, whether in the lungs (bronchial muscles) or in the liver (muscles of the gall-bladder and duct) have traveled out right into the muscles themselves and their inhibitory nerves come from the nerve cells of the sympathetic system.

Respiration is influenced by both sympathetics and parasympathetics, although the vagus is usually spoken of as the respiratory nerve.

Internal viscera, when compared with skeletal structures, have a relative paucity of sensory neurons, because of the fact that they lie deep in the body and are so shielded that it is not necessary to have the number or the wide variety of receptors for picking up and preparing defensive reflexes against many of the stimuli which affect structures on the surface of the body; for example, they need no nerves which will respond with pain to cutting, pinching or burning, because they are not cut, pinched or burned under normal conditions. But wherever we find efferent neurons belonging to a certain system, we also find afferent neurons of the same system to carry the stimuli, which arise in the structure in question, centralward; consequently, we have both afferent sympathetic and afferent vagal neurons in the pulmonary tissue.

EMBRYOLOGICAL EVIDENCE

Embryologically, the lung belongs to the gastrointestinal system, the same as the liver, pancreas and body of the urinary bladder. This fact is very important in understanding its innervation. It is formed from a diverticulum given off from the anterior portion of the intestinal tract.

Belonging to the intestinal tract the lung carries with it the innervation of the intestinal tract (Gaskell (10)).

In order to understand reflexes, it is necessary to know that the body of man is a segmented organism, having come up from the primitive

organisms in which every segment is more or less complete in itself, in that it has a nervous system to care for the body surface and the organs lying within the same segment. This is shown in figure 3, after Ross and Mackenzie.

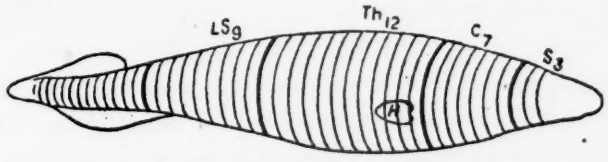

FIG. 3. DIAGRAMMATIC REPRESENTATION OF A PRIMITIVE VERTEBRATE ANIMAL

The Amphioxus, divided for convenience into three segments for the head, seven for the neck, twelve for the thorax, nine for the lumbosacral region, and an indefinite number for the coccygeal region. For clearness of comparison the heart (*H*) is represented as occupying the same position as in man, so that an adequate stimulus from the heart would cause pain in the distribution of the four upper thoracic nerves covering and protecting the heart. (After Ross and Mackenzie.)

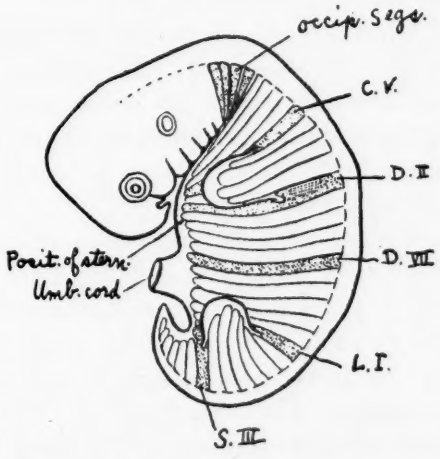

FIG. 4. DIAGRAM OF A HUMAN EMBRYO, FIFTH WEEK, SHOWING THE ARRANGEMENT AND EXTENSION OF THE MESOBLASTIC SEGMENTS

The first and last of each segment entering into the formation of the limbs is stippled (*C. V* and *D. II* and *L. I* and *S. III*). The position is indicated in which the sternum is formed. (A. M. Patterson.)

Man carries the same general plan, which is particularly shown in early embryonic life, as will be noted in figure 4. While, in the differentiation which has taken place, there are variations from the primitive plan, yet the segmental relationship between skeletal tissues and the splanchnic or

visceral tissues is preserved. A stimulus on the surface expresses its reflex most readily in that portion of the splanchnic or visceral system, and a splanchnic stimulus likewise expresses itself most readily in that portion of the somatic system with which it is segmentally related.

PHARMACOLOGICAL EVIDENCE

Pharmacological evidence of the innervation of the lungs is furnished by the use of adrenalin and atropine in their relief of the definite vagal syndrome found in asthma. The spasm of bronchial musculature is evidence of a predominating vagal activity. (Pottenger (11).)

This spasm is antagonized pharmacologically by two well-known remedies, namely, atropine, which antagonizes the vagus directly, and in this manner opposes the asthmatic attack; and adrenalin, which reinforces and increases the action of the sympathetics in their antagonism to the vagus, so that the asthmatic attack is relieved. (Meyer and Gottlieb (12), Eppinger and Hess (13), Pottenger (14).)

The affinity of adrenalin for the sympathetic system is manifested throughout the body. Physiologically, its injection produces sympathetic effects in all structures except the sweat glands. (Cannon (15), Gaskell (16).) This close relationship may be inferred from the fact that the medulla of the adrenal gland consists of modified nervous tissue which belongs to the sympathetic system (17).

While both atropine and adrenalin may fail to relieve the asthma completely, yet their action is nevertheless so uniformly inhibiting to the vagal activity found in the attacks as to make the innervation certain.

Another sympathetic effect is met in quite a group of asthmatics whose attacks are relieved by acute toxemia, such as that which accompanies tonsillitis and pneumonia. (Pottenger (18)(19).) This is significant because of the fact that toxemia expresses itself in many tissues as a stimulant of the sympathetics.

THREE IMPORTANT LAWS GOVERNING REFLEXES

Sherrington (20) laid down a law governing sympathetic reflexes which take place between visceral and skeletal structures, as follows:

> Taken generally, for each afferent root there exists in immediate proximity to its own place of entrance in the cord (e.g., in its own segment) a reflex motor path of as low a threshold and of as high potency as any open to it anywhere.

In order to explain the spreading of reflexes in the cord, Pottenger(21) formulated the following law:

The extent of the reflex is influenced by the strength of the stimulus. If the stimulus is slight it may pass over only those efferent neurons which are particularly adapted to it; but if it is stronger, the reflex spreads to other efferent fibres, either upward or downward in the cord over inter- and intrasegmental neurons. (As shown in figure 5.)

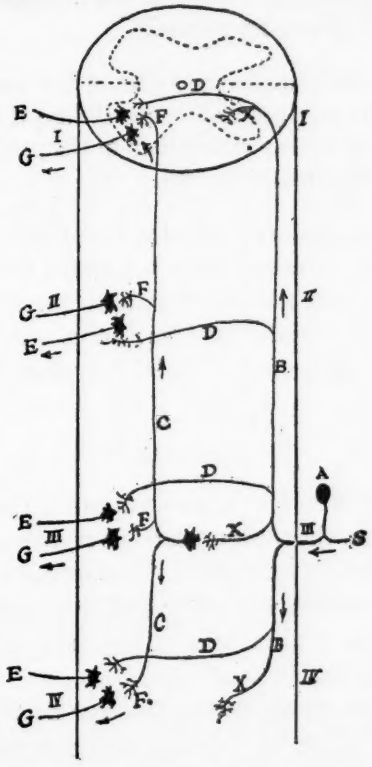

FIG. 5. SHOWING SCHEMATICALLY THE PATHS THROUGH WHICH INTRASEGMENTAL AND INTERSEGMENTAL REFLEXES ARE PRODUCED

The impulse is transmitted to the posterior root ganglion *A* over the sensory fibre *S*. From the ganglion *A* root-fibres *B* enter the cord which divide into ascending and descending branches. From these branches collaterals *D* are given off, which are transferred to the gray matter in the anterior horn and form synapses with motor nerves *E* to produce reflexes. Such reflexes occurring in the segment of the cord into which the root fibres enter, as indicated in segment III, are called intrasegmental reflexes. Those occurring in segments I, II and IV are intersegmental reflexes. Other collaterals *X* are given off from the posterior root fibres, which form synapses with association fibres *C*, which also divide into ascending and descending branches and give off collaterals *F*, which form synapses in the anterior-horn gray matter with motor neurons *G* to produce intersegmental reflexes.

The change in sensation (sensory reflex) from viscera is not a true reflex in the physiological sense, because it does not have a motor component to complete its action.

Visceral pain is usually spoken of as referred pain, although in the clinical sense it may be considered a visceral reflex, for in its localization it follows laws similar to those of the motor reflex, although there is no synapse in which the afferent neuron mediates with a motor neuron. Head (22) has suggested the following law to explain the expression of visceral pain in skeletal sensory nerves:

> When a painful stimulus is applied to a part of low sensibility in close central connection with a part of much greater sensibility, the pain produced is felt in the part of higher sensibility rather than in the part of lower sensibility to which the stimulus was actually applied.

In other words, when a painful stimulus is applied to the visceral tissues of low sensibility, it is transmitted centralward to the cord the same as it would be to produce a motor reflex; but, instead of being transferred to a motor neuron, it irritates adjacent nerve cells which give origin to sensory nerves belonging to the skeletal system in which the pain is expressed.

DISCUSSION

Sherrington's segmental law holds for most of the important organs of the body: for instance, the pleura, heart, liver, pancreas, stomach, intestinal tract, kidneys, and pelvic viscera. It does not hold for the lung, as I have described the reflexes clinically, and it is possible that it may not hold for certain other viscera, the reflexes from which we are not able definitely to describe at this time.

Figure 6 shows the sympathetic connector neurons which furnish the afferent paths from many of the important viscera of the body. With the exception of the lungs, the paths from which may be inferred from figure 1, each organ expresses its reflex motor sensory and trophic changes in the skeletal nerves which arise from the segment of the cord receiving the afferent impulse, according to the law of Sherrington.

After finding that the lung was an exception to Sherrington's rule, in that reflexes, which seem to be due to afferent impulses carried over the sympathetic nerves and which correspond to definitely accepted sympathetic reflexes in other viscera, are expressed in the skeletal tissues which

take their innervation from the midcervical portion of the cord; and particularly, bearing in mind the forward position of the lungs in their origin from the gut and also their position in the pharynx in early fetal life; and further, knowing that the central tendon of the diaphragm, which is so closely associated with the lungs, receives its innervation from

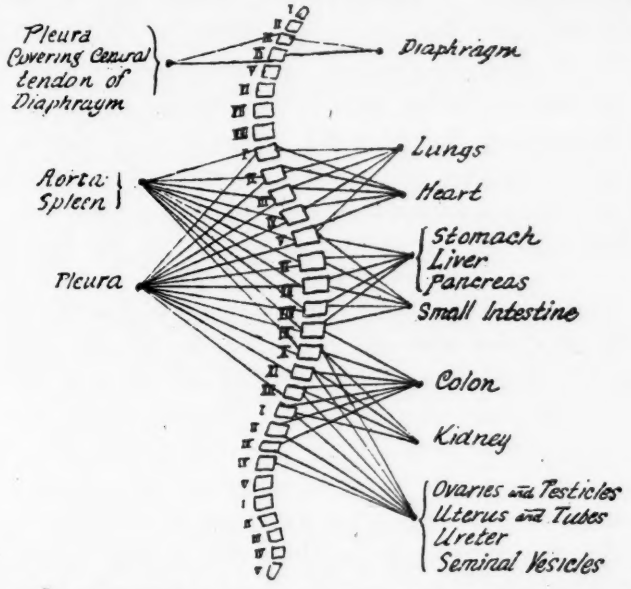

FIG. 6. THE CONNECTOR NEURONS FOR THE IMPORTANT THORACIC, ABDOMINAL AND PELVIC VISCERA

In the figure the connecting neurons are those which belong to the thoracicolumbar outflow, except those going to the diaphragm, which are spinal nerves (phrenics). The motor cells for the viscera are found in the various collateral ganglia.

The figure shows that the innervation of the various viscera may be divided into groups. The heart and lungs are innervated from practically the same segments, the upper Ist to VIth thoracic; the stomach, liver, and pancreas from the same segments, Vth to IXth thoracic; and the colon, kidney, and pelvic viscera from practically the same segments, IXth and Xth thoracic to IIId and IVth lumbar.

In spite of this grouping in innervation, each organ is brought in reflex connection with efferent neurons, both sensory and motor, which are more or less definite, in such a way that the motor and sensory reflexes do not overlap as much as might be indicated.

the cervical portion of the cord and expresses reflexes in skeletal tissues which are innervated by cervical nerves, I (23) suggested, in order to meet the conditions arising in pulmonary reflexes, that Sherrington's law be modified to the effect that impulses from viscera find efferent neurons

in segments of the cord *to which they are embryologically related* and with which they form reflexes most readily.

In classifying the pulmonary reflexes I found it a great aid that they could be differentiated from the pleural reflexes. Clinically, the pleura shows four sets of reflexes: through (1) the vagus of the parasympathetics, (2) the sympathetics, (3) the intercostal nerves, and (4) the phrenics. The reflexes mediated through the sympathetics, the phrenics and the intercostals all follow Sherrington's segmental law for visceral reflexes, in that the afferent impulse finds in the segment of the cord which it enters an efferent path through which it expresses its action most readily.

The fact that the upper intercostal muscles, receiving innervation from the upper six thoracic segments of the cord, do not show the pulmonary motor reflex, although the afferent impulses from the lung come back to those segments of the cord, is very suggestive of a transference of the impulse to other segments. The fact that we do find the motor reflex in disease of the lung expressed in the muscles innervated by the midcervical nerves would at least suggest that the impulse may be transmitted from the upper thoracic to the midcervical segments through intrasegmental paths. The further fact that the trophic and sensory reflexes from the lung, which correspond to the sympathetic sensory and trophic reflexes of other organs, are found expressed in the tissues innervated by the nerves arising in the midcervical segment of the cord, while the sympathetic, sensory and trophic reflexes, which arise from the pleura, are mediated through the thoracic nerves from the second to the twelfth, and that the reflex is usually limited to the area over the involvement, seems to indicate that pulmonary impulses are transmitted upward in the cord from the segments which they enter. Thus the localization of sympathetic reflexes from the lung can definitely be differentiated from sympathetic reflexes arising in the pleura.

There are several factors to be considered in determining the pathway of the reflex from the lung. I was guided by the same principle which applies to other viscera. Every internal viscus possessing a double innervation—sympathetic and parasympathetic—shows reflexes in which the afferent impulse is carried over both systems.

Sympathetic motor and sensory reflexes from the appendix, gall-bladder, stomach and duodenum (in case of ulcer), and kidney are quite well known. These all follow Sherrington's law in their distribution. No parasympathetic motor reflexes from any of these organs have been

described as occurring regularly in somatic structures in which the afferent impulse is conducted over the vagus. Headaches, however, have been described as parasympathetic sensory reflexes, in which the pain is mediated with the sensory fibres of the trigeminus.

As parasympathetic reflexes from the lung I have described reflex atrophy of the tongue, reflex atrophy of the facial muscles and a motor and trophic reflex in the sternocleidomastoideus and trapezius muscles, the impulses being mediated through the hypoglossus, facialis and accessorius respectively (24).

It will be noted that these reflexes all take place through the cranial nerves with which the vagus is closely associated. Gaskell, in his monumental work on the vegetative nervous system, describes the medulla oblongata as an expanded portion of the cord, and shows that there is the same relationship between the afferent visceral fibres and the motor neurons of the cranial nerves as exists between the sympathetic fibres originating in the thoracic and upper lumbar segments of the cord and the spinal nerves in the same segments. Therefore, we have the two pathways for reflexes: one set of reflexes having the afferent component in the sympathetic, and the efferent in the motor and sensory spinal nerves; the other having the afferent impulse in the vagus, and the efferent in the cranial sensory and motor nerves.

That there are parasympathetic motor and trophic reflexes expressed in the sternocleidomastoideus and trapezius muscles I early recognized; but I had not connected up the reflexes in other muscles of the shoulder girdle and the central tendon of the diaphragm, nor had I explained the pulmonary trophic and sensory reflexes, which express themselves in the tissues supplied by the midcervical segments of the cord as being of vagal origin. I had explained all of these reflexes as being of sympathetic origin, with the exception of the changes in the sternocleidomastoideus and trapezius, which I had considered as being of double origin.

Rasmussen (25), in discussing the reflex paths from the lung in a recent number of the AMERICAN REVIEW OF TUBERCULOSIS, accepts the opinion of Larsell (26)(27)(28)(29), that the chief source of afferent impulses from the lung is the vagus, and he suggests that vagal impulses mediate with the midcervical skeletal nerves to produce most of the pulmonary somatic reflexes. He quotes Larsell's work as showing that cutting the vagus nerve is followed by degeneration of practically all the nerve fibres in the corresponding lung. Larsell believes that the vagus gives us the chief nerve supply to the pulmonary tissue, but he recognizes that certain

restricted regions of the pulmonary pleura are supplied by some of the upper thoracic spinal nerves (probably meaning sympathetic). This would indicate that the sympathetic supply to the lung is of very slight importance. He quotes the works of Cajal and of Freeman (30), as showing that the sensory fibres of the vagus, after entering the upper portion of the medulla oblongata, send branches downward into the spinal cord as far as the third and fourth cervical segments, and he discusses the possibility of their mediating reflexes with the spinal nerves.

He also quotes Larsell's work to the effect that the sympathetic trunks are particularly connected with the pleura and that they, passing to the spinal cord over the corresponding dorsal routes, may send ascending fibres to the midcervical region and higher levels, which will mediate reflexes in the midcervical region, but he considers this possibility of comparatively little importance.

Reasoning from analogy in other viscera, as shown above, and also considering the importance of the sympathetic nerves in the relief of asthma, it seems to me that the importance of the sympathetic paths in the production of pulmonary reflexes is underestimated in Larsell's work.

Aside from reflexes which are definitely due to stimuli arising in the lung, we may have reflexes expressed in the neck muscles at times, as a result of severe inflammation of certain other organs. The muscles of the shoulder girdle will at times exhibit a motor reflex in cases of endocarditis, severe attacks of angina, and in acute pancreatitis; so will pain be expressed in the neck areas. While it is possible that the stimuli responsible for this anomalous location of these reflexes and those for the regular reflexes from the lung may course centralward over the vagus, yet the argument is at least equally convincing in favor of their being of sympathetic origin. The law governing the spreading of reflexes, quoted above, is sufficient in either case to explain the unusual location of the motor and sensory reflexes expressed in the nerves from the midcervical region in severe angina pectoris and acute pancreatitis, and also in explaining the vagaries found in the location of pain in diseases of some of the abdominal viscera and the kidney and bladder. Pain in the kidney is usually expressed in the back between the lower dorsal areas and the crest of the ilium, but often above the upper and below the lower limits. The same thing is true in pleurisy. While the regular area for pain is immediately over the point of inflammation, it sometimes extends much higher, and occasionally we find its expression lower, and even over the

lower areas of the abdomen. In the lower quadrant (on both the right and left sides) I have seen pain, which resulted from pleurisy involving the lower parietal and the costal portions of the diaphragmatic pleura (7).

Since the sympathetic nerves supplying the lung arise from the upper five or six thoracic segments of the cord, if the lung followed Sherrington's law its motor reflexes would be found in the skeletal muscles receiving innervation from the upper five or six thoracic segments of the cord; but such is not the case. They involve muscles which take their origin from the midcervical segments of the cord.

Since integration of action is one of the chief functions of the nervous system, and realizing that the various tissues and organs throughout the body are brought into harmony of action through the nervous system, and knowing the infinite number of paths in the cord through which this integration takes place through intersegmental as well as intrasegmental paths, and bearing in mind the manner in which reflexes are transmitted upward and downward in the cord when other organs are affected, it requires no stretch of the imagination to believe that the motor reflex from the lung differs in its expression from Sherrington's law only in that it is more complex; the impulses being transmitted to neurons in the segments of the cord which they enter, the same as in case of the other important viscera, which transmit them upward in the cord to mediate with motor neurons arising in the midcervical segments. This suggestion is strengthened by the embryological relationship of the lung coming off, as it does, from the anterior portion of the gut on a level with the pharynx; by its being associated with the pharyngeal structures in early embryonic life; and also by finding that the trophic and sensory reflexes from the lung are expressed in the same skeletal structures, superficial and deep, which receive their nerve supply from the midcervical segments.

Pulmonary trophic reflexes also occur in the same zones of the skin, in the same areas of subcutaneous tissue and in the same muscles which show motor and sensory reflexes. Inasmuch as these trophic reflexes in the tissues supplied by the cervical nerves are constant in chronic or healed pulmonary tuberculosis, the same as motor reflexes are found in both active, chronic and healed tuberculosis, and inasmuch as all of these sympathetic reflexes are found in definite tissues supplied by skeletal nerves from definite segments of the cord, and inasmuch as in the case of all other viscera these are the segments which receive afferent impulses from them through sympathetic nerves, therefore, I feel justified in de-

scribing this pulmonary reflex, even though it varies from Sherrington's law as a reflex of sympathetic origin.

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THE CHEMICAL ANALYSIS OF THE TUBERCLE BACILLUS[1]

TREAT B. JOHNSON AND ROBERT D. COGHILL

At a private conference held in Washington, D. C., October 16, 1925, which was called by the United States Public Health Service, the Bureau of Animal Industry and the National Tuberculosis Association, to discuss the question of the standardization of tuberculin, the writer presented certain fundamental principles of bacteriological chemical analysis, which must be followed out if the organic chemist is to be expected to unravel the chemical constitution of the tubercle-bacillus cell; to determine what is the most satisfactory substance for him to work with, and to establish what are the actual chemical foundations of tuberculin. The speaker wrote at that time as follows (1):

While we have to-day positive evidence of the existence of many of the cell constituents, such as proteins, fats, carbohydrates, etc., it is true that our knowledge of the actual composition of the bacterial cell is far from complete, and consequently we are unable to make an application of an analytical method which will reveal to us the true composition from a quantitative point of view. At this time it is quite apparent, and agreed by those who are interested in the development of chemical bacteriology, that a study of the chemical constituents of bacterial cells and of the products of cell metabolism is most important; but as long as the condition prevails that we have no thorough and severely tested method of analysis it will be impossible for the chemist to make any advance in this field, and we will remain in that state of chaos and chemical ignorance which prevails at the present time.

The following statement will also be found in the report made at the Washington conference:

In the carrying out of a line of research, such as is represented by our investigation of the chemistry of the tubercle bacillus, and directed toward a search for that respective fraction which will exhibit the highest tuberculin activity, it is necessary that the chemist have the closest coöperation of workers trained in certain fields of biological research. The development of any method for the separation and purification of an active tuberculin fraction cannot be

[1] Presented before the Pathological Section at the twenty-second annual meeting of the National Tuberculosis Association, Washington, D. C., October 7, 1926.

accomplished successfully without the assistance of experts who are competent to give accurate reports regarding allergic, serological, and cytological reactions of the various fractions which we succeed in separating. Unless such tests are made for us during the actual course of our chemical investigation, we are severely handicapped in the progress of our work, and no means are available whereby we can decide whether we are working in the right direction. It is necessary to have beacon lights to guide us in our course, otherwise we are likely to waste valuable time in unprofitable work.

After the completion of two years of research in the Yale Laboratory, which has been conducted in accordance with the principles and plans that have just been stated, it is now a pleasure and satisfaction to report at this meeting that our scheme of coöperative research has worked out successfully. Progress in the various researches has been made, and we have been able to add to our knowledge of the chemistry of the tubercle bacillus; we have also stimulated an interest in new and fundamental problems which did not prevail when we first undertook our chemical research work on this subject. While our major research problems have been developed to date through the application of a technique characteristic of the methods employed in experimental organic chemistry, we have, nevertheless, come to recognize more and more the fact, as our work progressed, that we can increase our chemical knowledge more rapidly, and steer more easily and efficiently our research course in a biochemical investigation of this character, by keeping in close touch with the progress of the researches of our coworkers in the border fields of science. In other words, we feel that we would not have realized so quickly the most important features and discoveries of our chemical work if we had not had the opportunity to benefit by the application of the present system or method of group activity in our tuberculosis work.

Our chief attention has been directed thus far to the study and development of a practical plan of analytical procedure which can be utilized successfully in the future as a base-line for bacterial chemistry. If we may judge accurately from the reports of our coworkers in the fields of cytology, serology, physiology and bacteriology, who have examined carefully the various fractions thus far isolated from the tubercle bacillus, we feel greatly encouraged and very hopeful of the results thus far obtained and of what our adopted analytical plan has opened up for us to investigate in the future. Not only have we been able to substantiate the soundness of our original conclusions and predictions, but as a result of our present analytical procedure we have revealed new and funda-

mental problems for further research, which would never have become known to us so quickly if some definite and practical line of chemical attack had not been laid out and followed.

It was not until we undertook to isolate definite organic combinations from the tubercle-bacillus cell in a state of purity that we first began to realize, as chemists, how complicated a mixture of chemical substances we were confronted with. On turning to the literature for help we were able to find very little data that would be of aid to us in our research. In other words, we were placed in the position of a pioneer on the frontier of an unexplored country and compelled to stake out a new claim, and begin a new development. Presented with such a confusing mixture as is present in a bacterial cell, we found it no easy task to develop a technique which would enable us to make out much at first in this jumble. In order to accomplish the object of our research, it was necessary to first gain a new vantage ground and establish a base-line from which to make a chemical attack with a finer precision than had been accomplished hitherto. In other words, it was necessary first to get behind the scenes, develop an original line of attack, and learn, if possible, something about the simpler chemistry of the cell. The information which we desire cannot be obtained with the microscope, nor by confining the attention of the investigator to the study of physical forms of cells.

From the very nature of the conditions under which bacteria grow and multiply by subdivision it would be predicted, from a chemical point of view, that one would find all stages of cellular development from the simplest combination up to the most complicated organic compounds in the growing bacterium. In some cases these changes in the cell are favored by aerobic and in others by anaerobic conditions. Complete synthesis of highly developed organic structures, such as proteins and aromatic combinations, are brought about within a few hours as the new bacterial cells develop. Therefore, one might expect to find evidence of every intermediate stage of organic development at all periods of cell-growth from the time of generation to its death. In other words, our chemical problem of bacterial analysis is complicated and rendered very difficult by the fact that a bacterium is always operating as a completely organized chemical system, undergoing constantly fundamental chemical changes and manipulating at very high reaction velocity, and with an accuracy and completeness that seem almost incomprehensible.

In the development of any procedure of chemical analysis of bacteria, we are also confronted with the phenomena resulting from autolysis in

the cells or their solution extracts. If enzymes are active and function in the bacterium during the preparation of the material for chemical analysis, the chemist is faced at once with a mixture of normal constituents of the bacterium with secondary products of autolysis. In other words, if he permits autolytic changes to take place, he is not obtaining data which reveal the true picture of the cellular composition or structure before its death.

In order to obtain, therefore, as accurate a picture as possible of the chemical composition of the tubercle bacillus, it was of course necessary to reduce to a minimum every possibility of cellular changes brought about by autolysis during any of our operations with the cell. Such changes begin very soon after the death of the bacterium. Also, it is known that certain constituents of bacterial cells, especially the contents of the lipoid fraction, are very susceptible to oxidation; and consequently erroneous results are obtained on analysis, if bacteria are exposed after removal from the culture medium to the atmosphere for too long periods.

Another treatment that led to erroneous results was the practice of killing bacteria by heat or, in laboratory language, by autoclaving. This brings about very pronounced changes in the constitution of the cell. Heating above 75°C. leads to coagulation of water-soluble albuminous constituents. Autoclaving also leads to other deep-seated changes in the phosphorus and carbohydrate linkages which are revealed by our methods of cell analysis. In other words, we have learned from experience that autoclaving at high temperature must be avoided if one expects to obtain accurate analytical results revealing the true chemical constitution of the tubercle-bacillus cell.

Before applying any process of aqueous extraction to remove water-soluble products from tubercle bacilli, it is necessary to remove, first, the fat and the waxy envelope which encases the microörganism. On removing these constituents of the cell it is very necessary, if one is to utilize the bacterial residue for the extraction of labile protein combinations, to operate under experimental conditions that will alter as little as possible the primary composition of the cell leading to coagulation or denaturation of protein. In our practice, we have depended on the use of cold ether for removing the fat. This does not remove all the waxy constituents, but it leaves the cells in an excellent physical condition for applying aqueous extraction later, to remove water soluble constituents. We believe that when defatting takes place under such conditions we are operating with the minimum danger of putrefactive or hydrolytic

change. We also overcome by such procedure any danger of infection by destroying the virulence of the bacteria. In applying water extraction to cells defatted in this manner we are able to accomplish very rapid and efficient extraction of soluble protein under sterile conditions, and are actually starting in our investigation with cytoplasm which has not been subjected to rough chemical treatment.

Only a small percentage of the proteins of tubercle bacilli are removed by cold-water extraction, and this seems to be the conclusion of workers with other cellular organisms. This fraction is coagulated by heat and, according to the results of the biological tests reported by my colleagues to our laboratory, it is the most potent tuberculin reagent that has thus far been separated from the tubercle-bacillus cell. It is precipitated from aqueous solutions at its isoelectric point with acetic acid, and dissolves in cold dilute alkali without immediate loss of its tuberculin activity. Prolonged treatment with alkali, however, is injurious. This water-soluble protein can be obtained free from carbohydrates and nucleic acid, and behaves in every way like a true albumin. Whether it is a single protein or a mixture of proteins we are not prepared to say. Also whether this protein fraction is identical with the active protein precipitated from tuberculin solution by ammonium sulphate remains to be established. Thus far no attempts have been made to compare our active protein and Dr. Long's protein either chemically or biologically. The fact being established that very active or potent proteins showing the characteristic tuberculin skin reaction can be obtained from both sources, it will be very important to decide whether a common protein constituent is the source of the specific activity. Before such a comparison can be made, however, it will be necessary to grow the bacilli in greater quantity in order to obtain this characteristic protein of the cell in sufficient amount for accurate chemical work.

It is very important to emphasize at this time the fact that all the tubercle bacilli used in these protein studies which we are discussing have been of one definite strain, and that it has been grown entirely on synthetic media of known composition. We have thus excluded, as much as possible, all variable factors influencing the results obtained; and this principle has been applied not only in the growth of the microorganism but also in the plan of treatment during chemical operations in the laboratory. This has led to a definiteness of chemical composition which it has not hitherto been possible to accomplish.

This active, water-soluble protein does not represent the chief amount of material extracted from the defatted cell by water. In fact, it represents only a small percentage. The largest proportion of the extractable material is comprised of material which will dialyze through parchment. All this material is nonprotein in nature, and represents an important fraction concerning which we have practically no knowledge at present. It will be one of our major problems this coming year to learn more about the character and composition of this fraction of the cell.

The major proportion of the protein of the cell is in a form insoluble in water but soluble in 0.5 per cent sodium-hydroxide solution at ordinary temperature. This fraction has been separated and analyzed. It has been reported to us as showing a very low tuberculin reaction. These

TABLE 1

N	WATER-SOLUBLE PROTEIN	ALKALI-SOLUBLE PROTEIN	
	per cent N of total	*per cent N of total*	
Humin	4.4	2.5	3.4
Amide	9.0	3.9	4.7
Bases	37.1	29.5	
Arginine	22.2	17.8	
Histidine	10.1	4.2	5.0
Lysine	4.8	7.0	7.5
Amino	39.8	57.6	63.6
Non-amino	6.5	4.5	

two proteins are distinctly different in their content of amino acids as is shown by the analyses according to the Van Slyke method. The most conspicuous differences are revealed by inspection of table 1. Both proteins contain sulphur.

Attempts to isolate a globulin fraction from the tubercle bacilli have thus far proved unsuccessful. Sugar combinations are present in practically all the extractive fluids of the cell. Thus far we have made no effort to advance our knowledge of these interesting sugar complexes. It is not improbable that some of them play a very important part in the specific immunity reactions of the tubercle bacillus and their study should be undertaken in the near future.

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THE VERNES TEST FOR TUBERCULOSIS

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The Vernes test for tuberculosis is based on the phenomenon of the periodic curve produced when blood-serum is combined with certain reagents. This phenomenon is of value in serological reactions when the reagent chosen is capable of producing a differentiating sinusoidal curve for pathological sera.

The successful clinical application of the test has been demonstrated by Jacquot and Uffoltz (1) in two of the offices of Public Hygiene in Paris, France, the Albert Calmette and the Edith Wharton Dispensaries, on a series of 1,240 specimens of blood. Our own limited observations were made possible through the courtesy of Dr. James Alexander Miller in allowing us to obtain blood from patients at Bellevue Hospital, New York City, and through certain researches carried out at the Institut Prophylactique in Paris. They leave a distinct impression of three outstanding features of the test.

First, being a flocculation reaction the many variables of the haemolytic system are eliminated, and, as it is a precise and mechanically controlled test employing delicately adjusted apparatus, the factor of the personal error is almost negligible.

Second, the results of the findings are recorded in such a manner that they are clearly, quickly and accurately presented.

Third, the reagent used is a nonspecific one, consisting of a pure chemical substance rather than an extraction from the growth of tubercle bacilli (*Mycobacterium tuberculosis hominis*), in which each of a series of harvestings may be subject to variations due to differences in infusions of broth and in ages and strains of microörganisms.

This test for tuberculosis has been carried out at the Institut Prophylactique, and has been made possible through its long experience with the Vernes flocculation test for syphilis, which, dealing with phenomena of the same nature, presents similar problems in its specific field. The chief apparatus employed in this new field of research is the *photomètre* of Vernes, Bricq and Yvon, used primarily for the test for syphilis,

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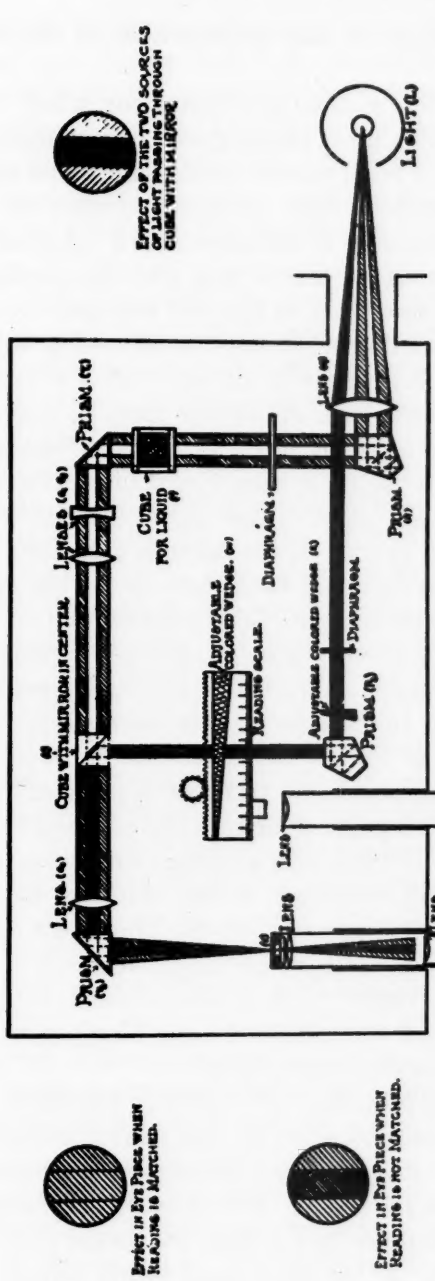

FIG. 1. PHOTOMÈTRE OF VERNES, BRICQ AND YVON, DESIGNED TO PERMIT THE READING OF FLOCCULATION IN TERMS OF MILLIGRAMS PER CUBIC CENTIMETRE OF A SERUM MIXTURE

and applied without change for the determination of the tuberculosis reaction.

The photometer (figure 1) consists of a metal box fitted with lenses, prisms, surcharges, and a wedge of fumed glass. It is designed to measure the loss of light from a beam passing through the liquid under observation, enabling the operator to read with great accuracy the degrees of flocculation, as a direct reading of milligrams on a calibrated scale attached to the movable wedge of fumed glass gives the precise measurement of the amount of absorption of light for one cubic centimetre of liquid. A complete description of this delicate instrument will be found elsewhere (2). It is not our purpose at present to deal with this subject in detail. Briefly, the light from an electric lamp L, passing through lens A, is divided by the reflecting prism P_1, into two beams, one beam reflected by prism P_1, through the cube F, containing the test liquid, and then reflected through lenses O_2 and O_3, to the mirrored cube C, which permits the lateral portion of the beam to pass through lens O_4, and enter triangular prism T_2, and from there to the eye-piece for the estimation of the absorption of light. The other portion of the original beam from lens O_1 passes through prism P_1, directly to prism P_2, where it is reflected at right angles, through the adjustable wedge of fumed glass with attached scale, to the cube C. The mirror insert in this cube reflects the central band of light in such a manner that it passes parallel with the light from the other source. Like it, it is reflected by triangular prism T_2, and brought to a point of focus in the centre of the eye-piece. The field of light in this eye-piece is of a briliant red, owing to the use of a color-screen. This field, composed of the beams of light from the two sources, is rendered homogeneous by the adjustment of the wedge of fumed glass. Thus the depth of the wedge required to render the field homogeneous is equivalent to the density of the liquid under observation, and the reading of the calibrated scale therefore represents the degree of absorption possessed by the liquid.

For the test itself, the procedure is as follows: The blood is obtained by venopuncture in the usual manner, not less than 10 cc. being collected in a tube. The tube is stoppered, and refrigerated over night to allow a complete separation of the serum. The blood is best taken when the patient is in a fasting condition and at least not sooner than three hours after the previous meal. It has been found in our experience that if, directly after taking the blood, the tube is placed in an inclined position and allowed to remain at room temperature for one-half hour before

being placed in the refrigerator, the contraction of the clot is more satisfactory, and a greater amount of clear serum is obtained.

After refrigeration the serum is decanted, and freed from cells by high-speed centrifugation. Two tubes are set up for each serum, one to act as a check against the other, and 0.6 cc. of serum placed in each of these tubes. The measurements may be quickly and accurately made by use of a mechanical syringe, the *rhéomètre* of Vernes. The reagent, consisting of a 1.25 per cent aqueous solution of resorcine ($C_6H_4(OH)_2$), is placed in a small glass beaker, and the control reading is made. It should first be ascertained that all liquids are at the same temperature, between 18 to 25°C. The procedure for the first reading is to place 0.6 cc. of the reagent by the use of the *rhéomètre* into the tube containing the serum. The tube should then be inverted several times against the thumb to assure a thorough mixture, and the liquid transferred to the chamber of the *photomètre* for the estimation of its absorption of light. This reading is made at once after the addition of the reagent, with the surcharges of the *photomètre* at *O/A*. The liquid is then returned to its respective tube and the tube closed with a rubber stopper. A similar procedure is followed with each tube, and these first readings are recorded for control purposes. The tubes are incubated for four hours in air or water-bath at a constant temperature of 20°C.

At the end of the incubation period it should be ascertained whether the *photomètre* is "reading" with the surcharges at *O/A* at the exact figure it recorded at the first or control reading, thus assuring perfect adjustment. If the adjustment is not the same and a different figure is recorded, the difference obtained is used in the final calculations.

The liquid is then transferred from the incubated tube to the chamber of the *photomètre* and reread for the degrees of absorption of light.

To interpret the test, the figure obtained in the first reading is used as a control figure and is subtracted from the figure obtained in the second reading after the period of incubation. The difference between these two readings represents the degree of flocculation caused by the reaction between the reagent and the serum, and is recorded in milligrams per one cubic centimetre of liquid.

Vernes (3) recognizes for practical purposes three zones in which the readings may fall. In the negative zone the final result may range between the figures 0–15. The intermediate, or doubtful zone, with readings between 15–30 is not diagnostic, but indicates the need of a careful revision of clinical symptoms. In this zone one must keep in

mind the possible reactions due to the starting of a syphilitic infection, grave septicemias, advanced cases of cancer, and possibly other acute diseases. However, if repeated tests fall into this zone and the clinical symptoms indicate a suspicion of tuberculous infection, one would become more certain of an early or of a latent inactive stage of the disease. While the other intermediate readings, not due to tuberculosis, do appear in this intermediate class, they do not continue to give this particular reaction for any length of time.

The third zone includes readings of 30 or above and these figures are diagnostic of a definite tuberculosis. This is the zone where the test assumes its important possibilities. By means of this reaction, the effects of the treatment, whether medical or surgical, may be estimated with great accuracy, and recorded in graphic form, indicating by the rise or fall of the flocculation on repeated tests the variations in activity of the tuberculous process, which may be quickly detected and easily interpreted by the clinician.

SUMMARY

1. The Vernes test for tuberculosis promises to be a distinct contribution to serological method in the diagnosis of tuberculosis and as a guide to treatment.

2. There are three outstanding features, in which it differs from the commonly employed tests, and which render it more accurate and more easily interpreted.

3. Owing to the precise technique and mechanically controlled apparatus, this test should tend toward more comparable and accurate results from one or several laboratories on serum from the same patient.

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THE SEROLOGICAL MEASURE OF TUBERCULOSIS[1]

ARTHUR VERNES[2]

The *Institut Prophylactique* of Paris after nearly four years has brought to a practical point a new seroreaction for tuberculosis. This reaction has given great service both for the early diagnosis and in the measuring of infection, which is estimated by means of a graduated scale reading from 0–150 and above. The service has been confirmed by so many investigators that we are led to present briefly this subject.

Without entering into the technical details, which have been made the subject of a communication to the Academy of Science of Paris, and several diverse publications (1), we may simply say that if one, under certain conditions, combines resorcine with human blood-serum there is obtained with tuberculous serum a precipitate which is not given with normal serum, and one can measure the diminution of transparency thus obtained with the tuberculous serum by means of a *photomètre*. The *photomtère* employed is the one that we have had constructed with Mm. Bricq and Yvon for the examination of syphilitic serum. The researches which we have carried out in serology during fifteen years are particularly those arrived at in the application of the phenomena of flocculation to syphilis and tuberculosis, and prove that this specific serological reaction is dependent upon the physical state of the fluid (molecular concentration, number and dimension of the elements in suspension, etc.). This has entailed the necessity of a precise regulation in order to obtain the best results from the fundamental phenomena.

When one combines human blood-serum with a reagent capable of producing a precipitate, the turbidity obtained obeys a law which is rather curious, and which has been verified for a considerable number of reagents. In taking the same amount of human blood-serum in a series of small tubes, and from the first to the final tube adding the reagent in a progressive curve, the turbidity observed from one end to the other of the series of tubes does not increase or diminish in a regular progressive

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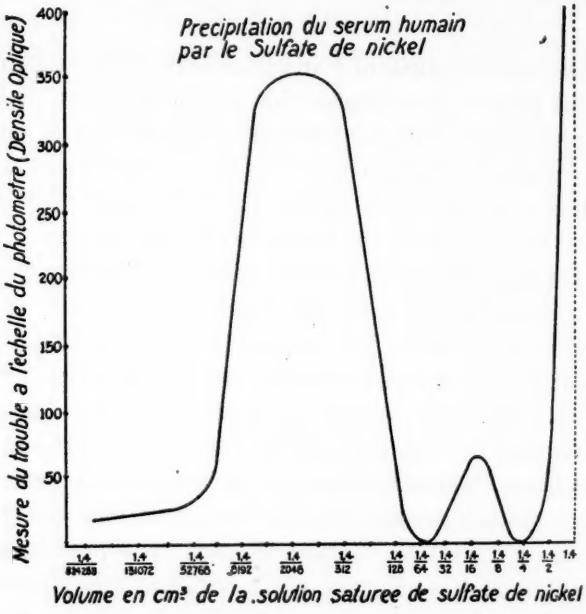
manner. On the contrary, there are waves, and the positions of the fall and rise are sometimes close together and sometimes at a distance, varying with the nature of the reagent employed (figure 1). The graph shows an example of this titre and the profile of the waves obtained when the



Volume of the saturated solution of sulphate of nickel in cc.	1.4 / 524,288	1.4 / 262,144	1.4 / 131,072	1.4 / 65,536	1.4 / 32,768	1.4 / 16,384	1.4 / 8,192	1.4 / 4,096	1.4 / 2,048	1.4 / 1,024
	1.4 / 512	1.4 / 256	1.4 / 128	1.4 / 64	1.4 / 32	1.4 / 16	1.4 / 8	1.4 / 4	1.4 / 2	1.4

Volume of unheated serum: 0.2 cc. in all the tubes.

Experiment: Set up a series of 20 tubes, 13 x 60 mm., and place in each 0.2 cc. of unheated serum starting from the right. Place in the first tube 1.4 cc. of a saturated solution of sulphate of nickel ($NiSO_4 \cdot 6H_2O$) in doubly-distilled water. In an extra empty tube place 1.4 cc. of the same solution and 1.4 cc. of doubly-distilled water, mix thoroughly, and place 1.4 cc. of the dilution in the second tube of the series. Add 1.4 cc. of the water to the remainder of the solution in the extra tube, mix, and of this add 1.4 cc. to the third tube of the series; continue this dilution and distribution successively, 1.4 cc. of the solution diluted to $\frac{1}{8}$ to the fourth tube, 1.4 of the solution diluted $\frac{1}{16}$ to the fifth tube, etc., the total volume of fluid in each tube being 1.6 cc.

The graph represents the measurement of the turbidity of the solution by the *photomètre* of Vernes, Bricq and Yvon, observed with the aid of a green color-screen. The reading is made for each tube immediately after the addition of the solution of sulphate of nickel.

reagent is a solution of sulphate of nickel. If one changes the reagent, the sinusoidal curve, as the mathematicians say, will change its form. Further, for a reagent happily chosen, the form of the curves may be modified by certain characters of pathological sera. The application of the result can then be made. A modification of the form of the curve can permit the identification of certain pathological modifications of the serum, because at the concentration at which the normal serum gives rise to an accentuated depression or even a complete absence of flocculation, a particular pathological serum may be capable of giving an accentuated depression or a marked precipitation. This precipitate, which is so important for the interpretation of the phenomenon, one must be able to observe by the aid of a suitable apparatus, which will register and measure the least change. On this general phenomenon of sinusoidal curve we have been able to base primarily a serological measure for tuberculosis.

Enough has been said for one to realize the necessity of respecting rigorously the conditions of the experiment which concern the proportions of the combination, the duration of the experiment and also the temperature, conditions which may considerably advance or retard the flocculation. The first condition is to assure a precise value to each of these elements in order to have the test successful. At the time of publication of our *fascicule iv* in April, 1926, our personal observations were based on over 6,000 examinations. Since then, the practical results of the method continue to be confirmed, giving at times results quite unanticipated by clinicians.

I will take for illustration a recent example of two cases occurring in the same week.

A new patient gave a photometric reading of 68 (indicating serologically a tuberculous infection). At a dispensary of the Office of Public Hygiene examinations of a most careful sort from a point of view of laryngeal or pulmonary infection continued to remain negative until attention was called to a mild pain in the lumbar region. The patient was then sent to the dispensary of a hospital for urinary diseases, where a diagnosis of renal tuberculosis was made, with tubercle bacilli found in the urine.

A second patient, on the other hand, was examined by a genitourinary surgeon, who on the basis of clinical symptoms established a diagnosis of renal tuberculosis and decided to remove the infected kidney despite the result of a photometric reading of 15 (which was not an indication of tuberculosis). Examination of the kidney after removal revealed no tuberculous lesions, but a papilloma of the kidney.

For the interpretation of the figures of the photometric scale a normal subject gives a reading from 0–15, a tuberculous one a reading over 30. Between these figures there is an intermediary zone, where one observes normal sera producing much flocculation or a tuberculous serum with slight flocculation. These figures include certain exceptions. One observes at the beginning of a syphilitic chancre a flocculation with resorcine, which is short-lived, and never again produced during the course of the syphilis. One can also observe a flocculation among certain cases of advanced cancer, and in the course of certain severe septicemias.

One must not lost sight of the distinction which should be made, in the reactions in tuberculosis and syphilis, between the independent factors of the blood and of the meningeal fluid, as, for example, in tuberculous meningitis an examination of the spinal fluid will give a photometric reading extremely high, while the blood-serum may register normal. We no longer record the cases in which our reaction shows the nonexistence of tuberculosis, but, on the contrary, when the reactions verify tuberculosis in subjects in which the disease is unrecognized, serology takes precedence of the clinical evidence. An important clinical control was made during May, 1923, by Drs. Jacquot and Uffoltz in two of the dispensaries of the Office of Public Hygiene of Paris. These results were published in *fascicule iv* of the works and publications of the Institut Prophylactique of Paris. We will limit ourselves to citing the conclusions.

The seroreaction has a most useful and practical application, particularly in the following instances:

1. To discover the concealed forms of tuberculosis (grippes, febrile gastric disturbances, bronchitis of ordinary appearance).
2. The evolution and prognosis of collapse therapy.
3. The nature of an empyema.
4. To determine the condition of an infection after a sanatorium cure, and the length of time the photometric reading remains lowered. This information will determine the course to take in the future (choice of sanatorium, duration of sojourn, etc.).
5. To determine whether the primary infection is arrested, this being important information for the individual and society, from the point of view of the rules of hygiene to follow, the choice of a career, of military service, etc.
6. In short, the seroreaction would appear to become an indispensable control for all attempts at the specific treatment of tuberculosis.

Such, in resumé, are the conclusions which we have been able to draw from the phenomenon of the flocculation curve for tuberculosis. It would be premature to speak of our researches on the same lines for cancer, but the application long since realized by us in the case of syphilis indicates the general scope of this phenomenon. For the researches to come, the serological problem presents itself as follows: Find for a given infection the reagent which determines, by a curve, a zone of differentiation corresponding to the malady considered.

Note: The technique for the examination of the blood is the subject of sufficiently numerous publications that we may consider our readers familiar with the test. That for the examination of the spinal fluid is slightly different. We have omitted the details of this difference in our article with M. Bricq and Mlle. A. Gager in fascicule iv. They are as follows: The resorcine solution should be 66 per cent, and one mixes 0.8 cc. with 0.4 cc. of spinal fluid, and this is incubated at 20°C. for one hour.

REFERENCE

(1) See in particular the works and publications of the Institut Prophylactique. Maloine, Paris, fascicules ii and iv.

THE REFRACTION AND COLLOID LABILITY OF THE BLOOD-SERUM IN TUBERCULOSIS[1]

JULIUS DE DARÁNYI[2]

ACTIVITY AND CONDITIONAL DIAGNOSIS

Since the researches of Nägeli, Hart and Franz, we know that almost every man is at some time in his life infected with tuberculosis. Owing to this fact, the so called "immune-diagnostic methods" for the determination of specific substances (antibodies), either by such well-known serum reactions as agglutination, precipitation and complement fixation or by allergic reactions, are not to be applied to a differential diagnosis. The more commonly used allergic reactions give no information concerning the gravity of the illness at all, because their positiveness is very often inversely proportionate to the gravity of the disease.

In treatment, also, the principal aim is not to cure the disease but to bring it to an inactive state. Although it is seldom that we have difficulty in deciding in the case of pulmonary illness as to whether it is tuberculosis, we have to determine the extent of its activity. Therefore, the conditional diagnosis (*Status-Diagnosis*), the actual situation, development and prognosis of the case, may be more important than the differential diagnosis. There is much discussion nowadays as to whether it would not be better to use the expression *progressing* instead of the terms *active* or *inactive*. Since the practitioner is the one primarily interested in the question as to whether the case is needing treatment and is infectious, Krömeke has very well suggested the use of the term, *actually needing treatment* (*zur Zeit behandlungsbedürftig*), for those who will not accept the expressions *active* or *inactive*.

Classical symptoms of activity, such as blood-spitting, positive sputum, fever, constant râles, are to be found in only a small percentage of active cases, and it therefore seems necessary to resort to other diagnostic methods, such as X-rays, the qualitative blood-cell determination, the

[1] Presented before the Clinical Section at the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 7, 1926.

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weighing of the body, etc. In determining activity, the physical colloidal chemical examinations have recently been coming more and more to the foreground instead of "immune-diagnostic" methods, which did not give the results anticipated.

DISPERSION OF PROTEIN COLLOIDS

The change in the colloidal chemical composition of the blood, resulting from tuberculosis, consists of an augmentation of globulins by processes accompanied by tissue destruction. It has long been known that in various infectious diseases the proportion of albumin and globulin $\left(\frac{\text{albumin}}{\text{globulin}}\right)$ varies; namely, that with the increase of the quantity of globulin there occurs a diminution in the protein quotient (P. Th. Müller, Erben). In tuberculosis we recognize an important sign of activity in the variation of this quotient (Alder).

Earlier authorities determined the albumin and globulin by gravimetric methods. Rusznyák described a procedure with nephelometry which, though simple enough, is not without many experimental errors. Nägeli and Rohrer worked with refractometry and viscosimetry, but their values are not exact for pathological sera. Lately Robertson described a method with both flocculation and refraction, but it was not acknowledged by Reis on account of the unequal and imperfect removal of protein substances. The exact quantitative determination of albumin and globulin is a very complicated procedure. Though figures are employed in working with these methods, their accuracy is by no means to be relied upon. Moreover, it is not so much the proportion of albumin and globulin that is important for our purpose, but the dispersion, that is, a change in the colloidal state of the serum proteins. Because of the augmentation of globulins, the molecules of which are larger than those of albumins, the circulating blood plasma is less dispersed. As to the dispersion, it is not enough to determine the quantity of both albumin and globulin, because, according to Sachs and Oettingen, we do not find a strict differentiation between the more and less dispersed protein substances with smaller or larger molecules. To be exact, one ought to fractionate the globulins further, to pseudoglobulins and euglobulins, since their quality is different, but that would complicate the method still more. Practically, the variation of the dispersion is much better expressed with a simple reaction than with complicated procedures. I

may also refer to Berger, who states, with regard to the serum structure, that the use of the so called colloid-lability reaction is more advisable than a complicated quantitative analysis.

COLLOID-LABILITY REACTION

In 1921 I pointed out that, with the decrease of dispersion, the flocculation of the serum through various physical agents is augmented; that is, the colloid lability becomes greater. So, as I showed, the colloidal equilibrium of the serum is disturbed in pathological processes with tissue destruction. I first demonstrated that the reactions of Klausner, Elias, Torday-Wilner, Bruch, etc., described as specific ones, are none other than nonspecific colloid-lability reactions. For the examination of the ability to flocculate, I found, after many experiments with various substances, that the best method was to mix the blood-serum with diluted alcohol and then to heat the mixture in the water-bath. This method gave a long scale of gradations from complete coagulation to flakeless negative reactions.

I will now briefly describe the reaction, together with certain modifications which I have made:

0.2 cc. of serum (active) is put in a long and narrow test-tube (12 cm. long and of 8-mm. bore) and well mixed with 1.1 cc. of diluted alcohol and placed in water at 62°–63°C. for twenty minutes. The dilution of alcohol is always to be freshly made from 96 per cent alcohol. To one cubic centimetre of it is added 4.1 cc. of a 2 per cent common-salt solution (it is always made freshly from a 20 per cent stock solution). The test-tube is to be examined immediately; and afterward at intervals of $\frac{1}{4}$, $\frac{1}{2}$, 1, 2, 3 and 24 hours following the heating in such a way that, when one stands before the window, one holds it up toward the ceiling, tilting it, but without shaking it, and looks for the flocculation with naked eye. All sera become opalescent, but agglutination, like flocculation, is found only in positive sera. One notes the time of flocculation, and only after twenty-four hours can its definite degree be determined. According to the later, or lesser, extent of cell disintegration, there can occur a complete or partial coagulation, a large or fine flocculation, or a flakeless negative reaction. The time taken for the flocculation indicates rather the quantity of globulin, and the size of the flakes their dispersion. A complete or partial coagulation is to be seen immediately; but a reaction with a flocculation in large flakes is to be examined after twenty-four hours, when one observes conglomerated unequal and large flakes by tilting the test-tubes. They are like a map and unhomogeneous in appearance when looked through in a vertical position. After twenty-four hours reactions with fine flakes yield flakes of 1 to 1.5 mm. at the most and the flakes are fairly equal and do not adhere to one another. If the test-tube is not tilted they appear milk-like and homogeneous. Negative reactions show no flakes macroscopically. The less the serum dispersion, the larger the flocculation. For the better development of the flakes in twenty-four hours, it is advisable to tilt all test-tubes at the intervals mentioned above. All test-tubes must be corked tight.

It is important for the reaction not to use more dilute alcohol than 96 per cent, and to work with the prescribed test-tubes and an accurate thermometer; otherwise we obtain too many negative reactions. Just as in the use of the refractometer, it is also important in this case not to take the blood after heavy meals. The reaction is not to be used if at the same time there are present other processes with tissue destruction, such as abscess, carbuncle, postpuerperal states, etc., which influence for many weeks the colloidal composition of the blood. Therefore, the above processes must be excluded.

Healthy people, as well as those suffering from hysteria, neurasthenia, functional diseases, and inactive tuberculosis, give negative reactions. In superficial, catarrhal processes, we mostly find a weak reaction ("twenty-four hours, fine flaky"). The strength of colloid lability increases with the extent of tissue destruction, so that we get a good quantitative measure of cell disintegration, especially in tuberculosis. Colloid lability is at least equal to the other symptoms of activity. When tubercle bacilli are demonstrable I have always found very strong reactions (for instance, "immediate to one hour, partial coagulation or large flaky").

Krömeke emphasizes that colloid lability is a more sensitive sign of activity than fever, blood-spitting, positive sputum, positive X-ray findings, etc.; however, it is sometimes negative in very early stages. Although he holds it difficult to differentiate active from inactive cases, Ritter also acknowledges that colloid lability is a valuable aid in ascertaining the need of treatment and in prognosis. According to Cahn-Broner, it is quite applicable in the determination of the intensity of tuberculosis. Krömeke considers the reaction with serum to be better than plasma reactions (Fahreus, Gerlócy, Starlinger, etc.) in the diagnosis of activity. Duzár is of the same opinion with regard to the reaction in infantile tuberculosis. The suitability of the reaction is also acknowledged by many others (Baum and Schumann, Pinner, Kausz, Herepey-Csákány, Sardo, Tinozzi, Lebinsky, Torday, Parassin, etc.). Krömeke even recommends a classification of tuberculosis into sero-active and sero-inactive forms, according to the colloid lability.

I found with Somogyi that skin tuberculosis, developed to the size of a quarter-dollar and without pulmonary disease, is sufficient to produce a positive reaction. But pulmonary tuberculosis generally has a greater influence on the blood than that of the skin, so that the reaction is more sensitive in the former case. A negative reaction rather excludes

open or bacillus-positive disease. Kausz found 100 per cent positive reactions in cases in the second stage (Turban). I have also determined the time occupied by the change of colloid lability. In purulent processes there is already a positive reaction after one or two days, as I have found in 10 different cases of carbuncle and *bulla phlegmonosa*. In such early cases of tissue destruction there was, at the beginning, a fine flaky reaction, which, after 4 to 5 days, became a large flaky one. An increase in the protein content did not take place at this time.

COMBINED METHODS

Efforts have been made to increase the applicability of physical colloid-chemical procedures by combining them, and with these methods to determine the protein-structure of the serum. Of course, they do not give a differential diagnosis any more than would a qualitative determination of the blood cells.

Starlinger first indicated the importance of the so called *protein-structure* (*Eiweissbild*). His method, however, is very complicated because of titration with ammonium sulphate and repeated centrifugation (28 per cent, one-half and completely concentrated solution of ammonium sulphate). Others, chiefly specialists in pediatrics, have occupied themselves with the so called *haemoclinical state* (*hämoklinischer Status*), in which they took up various physical and colloid-chemical reactions (Duzár), the sedimentation of red blood cells, viscosity, etc. Frisch recommended, besides refraction, the determination of fibrinogen, with which method we obtain very great values in pneumonic, exudative processes whereas in cirrhotic forms only medium values are found. Among the many combined methods may be mentioned the refracto-metric-viscosimetric method according to Nägeli, the determinations by Robertson or the specific viscosity by Rusznyák, obtained by thickening the serum with ultrafiltration to a 10 per cent protein content.

Since colloid lability gave the most reliable values of serum-protein dispersion, there have been attempts to utilize it as well in examining the blood-protein structure. Sardo, Duzár, Nassau, Hendelson, Baum and Schumann recommended series of examinations and titration with my method. Kremer used it combined with the determination of lipase. Deusch is also emphasizing the necessity of combining various methods. I have made comparative examinations with different physical methods, and have come to the conclusion that the method of colloid-lability can

be better employed when combined with that of refraction. From both refraction and colloid lability, one may judge the quantity and the dispersion of the serum-proteins, that is, the quantitative and qualitative protein-structure.

Alder was the first to indicate the importance of refractometry in tuberculosis. It gives very exact and constant values (Nägeli). Refraction gives approximately the protein content (Reis). I applied Pulfrich's refractometer (Zeiss) with Abbé's supplementary prism, for which one drop of serum was sufficient. One must stand the apparatus in water at 17.5°C. for five minutes. The values are given in scale degrees, which can be reckoned with a table into refractions and protein contents. First, I had to determine the normal values. Earlier experimentists have found fairly wide limits as normal values: for instance, Nägeli, 7.0–9.1; Reis, 7.42–9.13; Böhme, 6.3–8.8; Steinbrinck, 7.0–8.5 per cent protein-content. In my own experiments with 70 healthy persons, I found 62 (that is, an average of nearly 90 per cent) with a reading of 58–61 (refraction = 1.34947–1.35058, and protein content = 7.8–8.5 per cent with Reis's table). Therefore, values over 61 or below 58 can hardly be considered as normal refractions. But in children under twelve or fourteen years of age, when also healthy, there is hyporefraction (56–59), as shown in my examination of 15 children. The reason for my narrower limits of normal refractions than those of other experimenters is because the latter failed to take into account that the refraction may be very easily affected by various conditions. People who are slightly anemic or badly nourished often give hyporefraction. Persons with a slight occult purulent process (tooth abscess, carbuncules), convalescents, women after pregnancy or abortion, persons with skin diseases such as scabies and eczema, and very obese men generally give values with hyperrefraction (Löhr, Berger, Doerr). Anyhow, the above mentioned conditions, according to Pentimally, also affect the leucocyte formula of the blood for a longer time. Therefore, before applying the refraction values, the patient is to be carefully examined and questioned for the above conditions. In considering these facts, my refraction values conform, on an average, with the results of Winternitz with 7.81–8.49 per cent, and of Somogyi with 7.42–8.51 per cent normal protein-content.

REFRACTION AND COLLOID LABILITY

In chronic tuberculosis, the refraction increases (hyperrefraction), but decreases (hyporefraction) in the final stages, as proved by Alder and Petschacher. A high refractometric index is not a bad prognostic sign (Ciesynski and Peters). Although refraction alone gives valuable data about the illness, it is much better to apply it for diagnosis and prognosis in connection with colloid lability, particularly in serial examinations.

In addition to the former 115 cases, I have lately examined 75 pulmonary cases, of which 20 were grave and 30 quite slight. The rest, moderately grave cases with good prognosis, could be classified as Turban II. Moreover, there were 72 of lupus. Refraction and colloid lability were determined with all the sera. In the early processes I found normal refraction with the exception of 5 cases with hyporefraction. Most of the sera were kindly given for my disposition by M. Parassin, Director of the Dispensaries in Budapest. It seems that in the very early stages of the disease a low refraction can proceed to a normal or high refraction value. At the same time, when examining the colloid lability, I found that in 18 sera there was a fine flaky flocculation after one hour, and only in 3 cases a large flaky reaction within the same time. The latter cases were more acute and progressive. Moreover, two hyporefractive sera from the Red Cross Hospital gave large flaky flocculations. In these patients the disease was beginning so acutely that the sera were sent to me for a diagnosis of typhoid fever. On the basis of the protein-structure, I could exclude typhoid fever, because in the latter there is always with a low refraction a fine flaky colloid lability, as I shall publish separately later. Of 30 early cases the colloid lability was negative in seven, but in four of them the existence of an illness was very questionable. The general form of an early case may therefore be as follows: Refraction, 58–61 or less than 58; colloid lability, negative—fine flaky—large flaky (within one hour or over one hour), corresponding to the rapidity of the development.

Of the more chronic cases which can be placed in the Turban II class, I have examined twenty-five. The sputum was positive in four of them. All cases could be considered as benign. In accordance with other authorities, I found here high refraction values (greater than 61) in 23. The colloid lability was (as was also found by Kausz in his cases) positive in all cases. After the extension of the process the positiveness was

"fine" or "large flaky" or "coagulating." I was able to make a differential diagnosis on four occasions in this group. In two cases it was a question of renal tuberculosis or tumor. Malignant growths give mostly hyporefraction (Galehr) and fine flaky or negative colloid lability. Two cases have been proved as tuberculosis with a refraction of 62 and 62.5 scale degrees and a large flaky colloid lability. Once I excluded tuberculosis in the case of a little girl (Kétly Clinic in Budapest) with cerebral symptoms. Negative colloid lability made the diagnosis of tuberculous meningitis doubtful, and the autopsy proved the existence of a sarcoma. In another case at the Red Cross Hospital (Mrs. K.) the refraction and

TABLE 1

CASES	REFRACTION (PULFRICH'S SCALE DEGREES)	COLLOID LABILITY	
		Quality	Time
Healthy people	58–61	Negative	–
Early cases stage I (Turban)	Less than 58	Negative (about 20 per cent).	–
	58–61	Positive, fine flaky (mostly).	Within 24 hours
		Positive, large flaky (in some acute or rapidly progressing cases).	Mostly within 1 hour
Stage II	Greater than 61	Positive, fine flaky, large flaky, coagulating, in proportion to the development	Either immediately or within 24 hours
Stage III (feverish, excluding colliquative cases)	Less than 58	Positive large flaky or coagulating	Within 1 hour

colloid lability decided the diagnosis in favor of a *pleuritis callosa* and not a carcinomatous pleura (refraction, 63; colloid lability, large flaky in 15 minutes).

I had the opportunity, through the kind permission of Professor Okolicsányi-Kuthy of St. John's Hospital (tuberculosis pavilion) in Budapest to examine 20 grave febrile cases with positive sputum reports. Seventeen of them showed a low refraction (less than 58), two a normal refraction, and one a high refraction (greater than 61). In all these patients the colloid lability was very strongly positive; namely, large flaky

and sixfold coagulating reactions. Usually we do not find any augmentation of the protein content in cases with a bad prognosis, which are usually normal or subnormal. Also, one rarely finds in grave cases a colloid lability with fine flaky flocculation. Low refraction, therefore, with a large flaky or coagulating colloid lability may be regarded as a cachectic reaction.

The results are summarized in table 1.

I also made serial examinations of 6 cases at two to four-week intervals. The patients were treated in the Department of Professor Okolicsányi-Kuthy and in the Red Cross Hospital. One case which ended fatally was especially instructive: *Countess S. I.*, 20 years of age: October 20, 1924, refraction, 58; colloid lability, large flaky (15 minutes): November 15, 1924, refraction, 57; colloid lability, large flaky (immediately): December 20, 1924, refraction, 55; colloid lability, partial coagulation. The patient died in the early part of 1925. The following is another case: *N. B.*, 25 years old, male, Turban II: October 5, 1924, refraction, 62.5; colloid lability, large flaky (15 minutes): December 10, 1924, refraction, 60; colloid lability, fine flaky (3 hours). The case became inactive.

In all the 6 cases, the refraction and colloid lability were changing with the development or healing of the disease, thus conforming to the results of the clinical examinations. The formula of the alteration of refraction and colloid lability in a case with a good prognosis, in a series of examinations, is as follows: *R:* $>61 - <61$ (>58). *C. L.:* (coagulating)—large, then fine flocculations—negative. *Characteristic features:* The diminution of the *R.* and *C. L.* In cases with bad prognosis: *R:* $>61 - <61 - <58$. *C. L.:* (fine flaky)—large flaky—coagulating. *Characteristic features:* The diminution of the *R.* with augmentation of the *C. L.* Thus the inverse progression of *R.* and *C. L.*, especially in cases with hyporefraction, indicates a bad prognosis.

The coherence of refraction with colloid lability in prognosis was the most obvious in lupus. I examined 72 cases with Somogyi, in 64 of which we found a high refraction. Protein augmentation was not found in 5 cases in which the area of disease was small; further, in 3 cases complicated with grave lung processes there was a low refraction. In more solid skin tuberculosis, one obtains fine flocculation; in advanced cases with fistulas and exudations, large flaky reactions.

When phrenicotomy is indicated, Herepey-Csákányi emphasizes the importance of the colloid lability. Cases with a low refraction and large

flaky colloid lability (especially in serial examinations) show a bad prognosis and are not fit for operation. Also, as an indication for artificial abortion, only cases with low refraction and large flaky colloid lability can be taken into account (examinations on these cases were made in the Bársony Clinic in Budapest).

From the form of the flocculation one can deduce the nature of the process. I have found (as Deusch has found, in the sedimentation reaction of the red blood cells, the highest values in exudative pneumonic cases) that these forms of tuberculosis produce strongly coagulating or large flaky reactions, whereas usually one finds fine flaky reactions in productive cirrhotic cases. Naturally, refraction completes the colloid lability because a large flocculation in a serum with a low refraction has a different meaning than if a serum with a high refraction shows the same strength of flocculation.

The origin of the serum proteins, especially that of serum-globulins, is uncertain. It has been proved that the refraction diminishes in processes with a protein loss (pregnancy, malignant growths, acute contagious diseases, colliquative tuberculosis, etc.).

In cases of tuberculosis, the body is able to recover the loss until its function is intact and then the protein loss will be overcompensated (hyperproteinemia). But in the case of an excessive protein loss or in a weakened body, recovery is imperfect and leads to a low serum-protein content (hypoproteinemia). The restoration is obtained through large molecular proteins, that is, globulins, passing into the circulation. In this way the dispersion of the serum is diminished.

SUMMARY

1. The colloid-lability reaction indicates the activity of the tuberculous process. The determination of both refraction and colloid lability of the serum can be well applied in the conditional diagnosis and the prognosis, especially by means of serial examinations. From the refraction one can estimate the quantity, and from the colloid lability the dispersion of the serum-proteins. Both values express the protein-structure (*Eiweissbild*).

2. In incipient cases refraction is still normal, and colloid lability in most cases, if not strong, is already positive. In chronic tuberculosis both values are increased. In grave cases, we mostly find low refraction values with very strongly positive colloid lability.

3. In serial examinations, the increase of refraction and colloid lability means a progression of the tuberculosis, and the decrease of both that

healing is taking place. An increase of colloid lability to strongly positive reactions, with a diminution of refraction, that is, an inverse progression of both values, indicates a bad prognosis, especially if hyporefraction values are reached.

THE SOCIAL IMPORTANCE OF HELIOTHERAPY IN SURGICAL TUBERCULOSIS[1]

A. ROLLIER[2]

More than twenty years' experience with heliotherapy in the treatment of surgical tuberculosis permits us to affirm that this treatment realizes to the highest degree the aims of orthopaedics and conservative surgery. It enables us to dispense with surgical intervention, so often the cause of irreparable mutilation. By preserving the maximum of articular function, developing the musculature and restoring to the body the harmony of its outlines, it gives back to the world individuals no longer maimed and deformed, but normal and vigorous, and capable of working for their living. Thus heliotherapy acquires, for this reason alone, an incomparable social value.

It is well known that the gravity of a tuberculous affection depends not alone on the degree and extent of its anatomical lesions, but, above all, on the state of defense of the organism attacked. Therefore, a rational treatment of tuberculosis should not limit itself to the local foci. To the local manifestations of a general diathesis one must apply a general therapy, aiming first of all at improvement of the whole condition, and combining with it a local treatment which interferes in no way with the indispensable rehabilitation of the whole organism.

Heliotherapy adequately fulfils this double rôle. It is really no more than a return to the laws of Nature, from which we are divorced more and more by our ultracivilization and unnatural conditions of life.

By giving our patients the benefit of those life-factors, air and sun, we are placing their defective organisms in ideal conditions for defense, drawing from Nature itself, *Natura medicatrix* so dear to Hippocrates, the essentials of health, which she lavishes upon us with untiring generosity. In association with the air-bath, in itself a real tonic at an altitude, the general sun-bath, that is, the direct action of the sun on the

[1] Presented *in absentia* at a session on *X-ray and Heliotherapy* before the Clinical Section at the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 5, 1926.

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total surface of the integuments, constitutes the most energetic of reconstituents. Further, the sun-cure realizes the perfect local treatment by virtue of the analgesic, bactericidal, alterative and sclerogenic action of the solar radiations.

Guided by these principles, and encouraged by the results obtained by putting them in practice, we were logically led to condemn surgical intervention, which not only does not aid in improving the general condition, but too often compromises it and at the same time injures the local defense and favors the dissemination of disease-germs. For the same reasons we have condemned the sealed-up plaster cases which, by depriving the diseased regions of the body of air and sun, hinder the local process of healing, destroy the important physiological functions of the skin, cause atrophy of the musculature and bony skeleton, enfeeble the organism, and, to sum up, are in opposition to all physiological and orthopaedic good sense.

We have replaced them with a rational orthopaedic, the very simplicity of which has revolutionized in no small degree the methods formerly in vogue, and which aims above all at the minimum of interference with the general treatment. Heliotherapy, in the light of what has been said, and applied with a rigorous dosage of which we have established the rules, fulfils all the conditions required of a treatment for tuberculosis, both general and local; it is seen to have not only a therapeutic and prophylactic importance of the first order, but an incomparable social value.

It is on this last, and perhaps less-recognized merit of heliotherapy, that I should like to insist to-day. The action of the sun-bath, that is, the methodical exposure of the integuments, on the organism is multiple. First, there is its action on the skin, which gains in tone and pigments progressively when it is placed in immediate contact with the air and sun, its natural *milieu*. It regains its many important physiological functions (indispensable for the normal life of the organism: protection, innervation, excitation, elimination), and becomes once more the real garment provided by Nature. Pigmentation confers a progressive resistance to heat and cold, and prevents the penetration of disease-germs. Further, it appears to behave in practice as a sort of accumulator; that the resistance of the patient is in proportion to his pigmentation is a fact of every-day experience, and pigmentation seems to act not only by protecting the skin against excessive irritation from the ultraviolet rays, but also by regulating the heating effect of the sun.

The biological value of pigment becomes every day more evident: very probably it receives, supplies and activates the essential elements of the hormones.

The general sun-bath, by dilating the capillaries, determines a flow of blood from the depths to the surface through the muscular layers: it stimulates and regularizes the circulation better than the best massages, and admirably restores the musculature. This restoration of the muscles is probably due to the continuous tonic action on the muscle fibre, consequent upon the vibratory shock which the solar radiations determine in the close network of sensory nerve-endings of the skin.

By restoring to the muscles their original firmness and tone, the sun-cure reëstablishes or reinforces the action of the muscles on the bony levers, and favors, by an eminently physiological process, the return of articular function. The action of the sun is also felt on the ligaments, and manifestly stimulates the recalcification of the entire bony skeleton. This characteristic, which I had pointed out from the beginning of my work, not only for tuberculosis but also for rickets, has been brought to light again by the remarkable researches of Hess and his collaborators, Huldschinski, Lesné, etc.

The tonic action of the sun manifests itself also on the thoracic and abdominal organs. The air and sun-bath, particularly at an altitude, revives the appetite, stimulates the digestive functions and gives new life to the vital forces. Under its influence the number of red blood corpuscles increases, as well as the haemoglobin content of the blood. The blood formula improves, and the metabolic exchanges become more active. The blood is transformed, in some way, by the light absorbed into a reservoir of radiant energy. Carried throughout the organism, it stimulates the intracellular mechanisms of oxidation and reduction, thereby modifying its general metabolism, increasing its power of resistance and making it, by a natural immunization, a better instrument for the cure of tuberculosis. Finally, I would point out the favorable action of the sun on the internal secretions; the therapeutic power of the sun on affections of endocrine origin proves the stimulating and regulating action of the radiations on the hormones (internal secretions).

While, then, heliotherapy may be considered the best general treatment of surgical tuberculosis, it also constitutes, as I have already said, the perfect local treatment, thanks to the analgesic, bactericidal and sclerogenic action of the sun's rays. Combined with immobilization and

extension, it rapidly diminishes and finally banishes the pain in all forms of tuberculous osteoarthritis. This is also true of peritonitis and cystitis, when sunlight is carefully dosed. Further, the solar radiations cicatrize chronic wounds resistant to other treatment and provides for them the ideal dressing, destroying, as it does, the infecting bacteria better than the best antiseptics, while leaving uninjured the cellular resistance. This powerful sclerosing action of the sun is not limited to superficial foci: bone and joint lesions, however deep and at whatever stage of their evolution, react to heliotherapy.

Our radiographic controls covering about 50,000 plates prove that no bone lesion escapes its action. In Pott's disease, whatever may be its position, one sees the progressive sclerosis of extensive vertebral lesions, the disappearance of the accompanying cold abscesses or the calcification of their remains; solid blocks are built up, intervertebral bridges are formed, and these latter provide a more efficient aid to consolidation than the most perfect bone-graft. In hip disease, whether in adult or child, even when the acetabulum, the head and often the neck show signs of extensive destruction, shown on an X-ray plate by a cloud obscuring the outlines of the articulation, one sees the gradual reappearance of order out of this chaos. A new joint cavity, a new head form by degrees, and their outlines, at first confused, take on an ever-increasing precision. The zone of demarcation becomes increasingly clear, and the atrophied parts are the seat of an intense recalcification. In other cases, in which the femur has perforated the caseous floor of the acetabulum, the X-ray plate marks the stages of reconstruction of a strong partition of trabecular structure, rough at first, but later compact and regular. A new articular cavity is formed, so perfectly sclerosed and delimited that the femoral head attains an unhoped for functional adaptation. We have witnessed similar and equally unhoped-for transformations in the X-ray pictures of tuberculous osteoarthritis of the knee, shoulder, elbow and wrist. In the knee, for instance, even when an osteoarthritis has destroyed the cartilages and articular surfaces, the reconstruction of the eroded surfaces and cartilages is frequent, and we have seen it go as far as *restitutio ad integrum*.

In bad cases of spina ventosa, we have seen entirely destroyed phalanges show, after cure, a structure so dense and compact that one could not distinguish them from their normal fellows. We have also series of plates showing the successive phases of the spontaneous elimination of sequestra, thus demonstrating the natural process of demarcation,

which it is in the interests of the organism to establish between the healthy and the diseased parts.

The sun-cure at an altitude is not only the best treatment for surgical tuberculosis, but exercises also a valuable psychotherapeutic influence on the patient's morale. This is particularly the case when it is combined, as it is usually in the majority of our establishments, with regular and methodical manual occupation.

Guided by this principle, that in surgical tuberculosis absolutely rigid immobilization is an error prejudicial to the organic defense, we first replaced, as we have already seen, the unwieldy plaster cast with simple apparatus, which immobilizes the diseased articulation only, giving freedom to the other joints. Subsequently we endeavoured to develop the specific resistance of every patient, concomitantly with his general resistance, by encouraging the practice of manual work, progressively and carefully adapted to each individual. It soon became evident that this manual occupation was a real therapeutic factor in the cure of tuberculosis; and we were thus led to recommend the work-cure, strictly individualized as a general measure capable of rendering valuable aid, and the results have been every year more convincing. The work-cure is of course carried on in the sun whenever possible, but is suitable for any weather. Further, it has a double advantage, moral and material. It is a powerful protection against boredom, that disease of the soul, as Dr. Vigné says, "A serious disease, though it has no name in pathology." Besides its therapeutic and moral influence, the work-cure offers to our poor patients a by no means negligible financial aid. Carving, lace-making, basket-work, ornamentation on tin and leather, typewriting, toy-making, etc., such are the principal occupations of our surgical cases, according to their individual tastes and aptitudes. The financial result of their work is by no means negligible: a sale, organized in February, 1926, of the things made by our patients and convalescents, yielded the respectable total of 10,000 francs, of which every penny was divided among the workers. We prescribe also this work habit, manual and intellectual, for the children in our clinics. Lessons are given to all our children, whether bed-cases or not, (except at the beginning of treatment, when such as are weak or feverish are excused) on the galleries open to the sun and air. This breaks the monotony of the cure, gives an aim to the long hours of leisure and an interest to life, and encourages in the children a healthy emulation.

The morale of our patients is wonderfully sustained by the regular use

of the sun-bath. The cases of surgical tuberculosis that come to the mountain present for the most part a bad general condition. Weakened by long periods in the hospitals below, or by repeated operations, discouraged by the failure of former treatments, they have lost all faith in the possibility of cure, and, even worse, the will to be cured. One must treat the spirit as well as the body, and heliotherapy, used first alone, then in association with the cure, helps us in the most wonderful way. The brilliant sunlight, winter and summer, in the mountains, gives the patients all that profound and intimate satisfaction, which comes from the renewed activity of the faculties,—as it were, an expansion of the whole being. This spiritual rebirth of the tuberculous patient on the mountain is undeniable: we see it every day. It is for the doctor an invaluable auxiliary, for it simplifies for him the psychotherapeutic side of his work, so necessary in chronic disease, and collaborates in the interest of the patient. Thus, by the careful combination of the sun-cure and the work-cure, with their double influence, psychological and physical, on the patient, we realize successfully that rational therapy of healing Nature, which aims at the active immunization of the organism, by stimulating the natural forces of defense against the infectious agent. But the cure of surgical tuberculosis is but half the battle: the ground gained must be consolidated, and for this reason the after-history of our old patients has been a constant source of anxiety. Too often, convalescents, and particularly those without means, return to unhealthy houses, workshops or factories, where the hygienic conditions are such that relapse is a constant danger. The best way of assuring the tuberculous patient against a return of his disease is to maintain his general condition in a state of vigorous defense. Sun and air remain always the great protectors of the organism, and to enable him to take full advantage of them, the old tuberculous patient should renounce forever the city life which caused him to develop the disease.

With this in our minds we started in 1903, in collaboration with Pastor Hoffet, the work colony, which enables our old patients to complete their cure and maintain their refound health at a very slight cost, which is partially covered by the product of the work.

This return to work, excellent as it is for the morale of the patient, reacts also on his physical condition. The tuberculous patient, by regaining the taste for work, loses that depressing feeling of his own uselessness and wins a new self-confidence. This is for him the first stage on the way back to a normal life.

The striking results given by the work-cure in our poor clinics have encouraged us to consider the possibility of its more extended application at Leysin, in the shape of a model manufacturing clinic reserved for patients without means and for convalescents. In such a clinic patients could occupy themselves with appropriate manual work, while continuing to benefit from the helio-alpine treatment, and the product of their work would go to their upkeep. This would be perhaps the best solution of the financial problem, which so often complicates the treatment by heliotherapy of necessitous cases.

From what has been said above, the conclusion may legitimately be drawn that heliotherapy, systematically applied, is capable of bringing about a real resurrection in organisms profoundly undermined by tuberculosis. A splendid general condition, a new skin, the resistance of pigmented integuments, and a complete reconstitution of the musculature, which often endows former cachectic patients with the bodies of athletes,—such are the characteristics of cures by heliotherapy. But the rôle of heliotherapy is not only curative. If it has shown itself able to conquer surgical tuberculosis in all its stages, it seems evident that, *a fortiori*, it should be able to prevent its onset. Our experience has amply proved this hypothesis. It is well known that tuberculous infection generally occurs during childhood. It has been proved that at the age of puberty 95 per cent of children have paid their tribute to tuberculosis. Since, then, the seeds of the disease are laid in childhood, it is during childhood that we must fight it and reduce it to impotence. To this end the resistance of the child must be fortified to the maximum, and everything avoided which might in any way diminish it. Experience has shown that there is no surer way of obtaining this result than the air and sun-cure combined with rational exercise. We have carried out since 1900 this preventive heliotherapy in the *School in the Sun* at Cergnat, near Leysin. This simple experiment of lessons given in the open air and sun has shown us what a striking improvement may be expected in delicate and predisposed children. After a few weeks, sickly children with narrow sunken chests, flabby limbs and atrophied muscles, undergo a striking transformation. Bronzed skin and fresh complexion replace the anaemic pallor; the general condition is toned up, the haemoglobin percentage steadily mounts; flabby muscles become firm and the chest expansion is increased; while the X-ray shows a progressive sclerosis of tracheobronchial lymph nodes. An awakening

of the intelligence goes hand in hand with the development of the body; the *joie de vivre* is evident on the sunburnt faces of the children.

We have carried on, ever since, a campaign in favor of the air and sun-cure prophylactically applied. Open-air schools, as you know, are spreading in all countries; and, though I cannot here deal with all the experiments carried out in this domain, I must at least mention the remarkable preventive work of Doctors Jeanneret and Messerli at Lausanne, and in France the persevering campaign of Dr. Armand-Delille, so fertile in results. I should like, in passing, to pay my tribute to the United States, which has so often shown us the way in preventive medicine as in so many other fields.

We hope to found in Switzerland a rational and systematic prophylaxis in the schools, not only in the open-air schools, which are after all the exceptions, but also in all the orphanages, *crêches*, in the soldier's barracks, in the cities, and above all in the schools in general. The public school is too often a place of physical deterioration, where the mind is cultivated at the expense of the body, instead of providing an ideal opportunity of giving to the children, under a common discipline, an education in solar hygiene, from which they would benefit all their lives.

The school, as we conceive it, would thus attain that ideal cherished by the ancients, *mens sana in corpore sano*, and it is not perhaps too optimistic to hope that by improving the health of the body the improved health of the soul will follow.

The pursuit of a regular life of discipline and work in the open air and sun frees the child's spirit from many a harmful preoccupation. In the *School in the Sun* he learns to read in the sublime book of Nature. As the body becomes stronger, the intelligence blossoms, the character is moulded, and the soul awakes. The simple and hygienic existence, which we recommend, develops in our children nobler and more virile aspirations.

Thus, when we reckon up the results that heliotherapy has achieved in so many different domains, when we reflect on the blessing it could confer on humanity if it were better understood and more widely applied, we are compelled to admit that this method of treatment has a considerable social importance,—at least one that is equal to its therapeutic value. For, as we have seen, it not only enables society to recover that human capital of which tuberculosis had deprived it,

but it prevents the onset of the disease in the young, thereby contributing to the formation of new generations, healthier and more resistant both morally and physically. This claim alone justifies us, I feel, in considering heliotherapy as one of the most fertile acquisitions of modern medicine.

FIGURES

PLATE 1

A. Child who arrived with 34 lesions of tuberculosis: osteitis, periostitis, adenitis, multiple sinuses; tuberculosis of both feet, right hand; peritonitis; advanced tuberculosis of the left lung. General condition very poor. Advanced cachexia; high temperature; albuminuria.

B. The same one year later, all the tuberculous foci cured.

C. The same two years later on his skis.

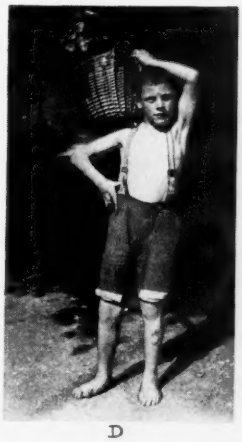
D. The same ten years later, his cure having been completely maintained in spite of the boy's having lived all these years of the war in a German orphanage, where he underwent considerable privation.

E. After 20 years; gardener; able to earn his own living by his work; keeps in perfect health.

A

B

C



D

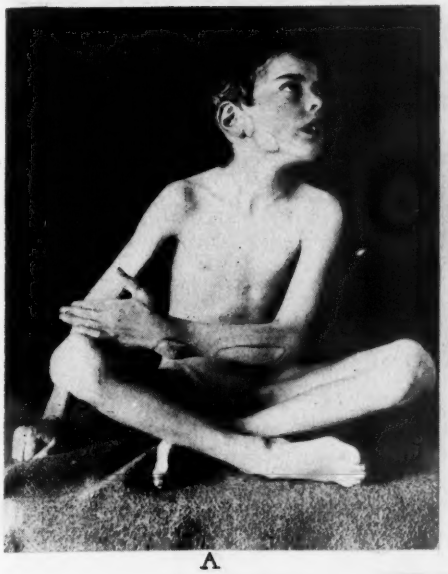
E

PLATE 2

A. A boy who had 17 tuberculous lesions: osteitis, periostitis, adenitis. One lesion of the temporal region had been curetted. Secondary infection, sinuses, affection of the tracheobronchial lymph nodes and infiltration of the right apex.

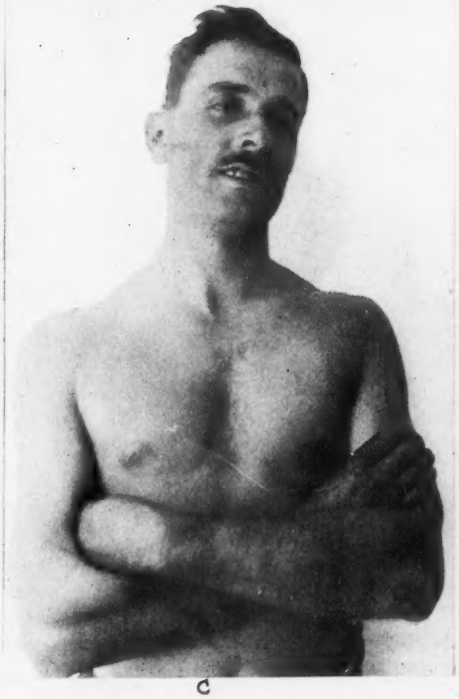
B. Complete cure 6 months later.

C. The same, 16 years after his cure; wheelwright and agricultural laborer. Did more than one year's military service without one day off. Condition of health perfect.



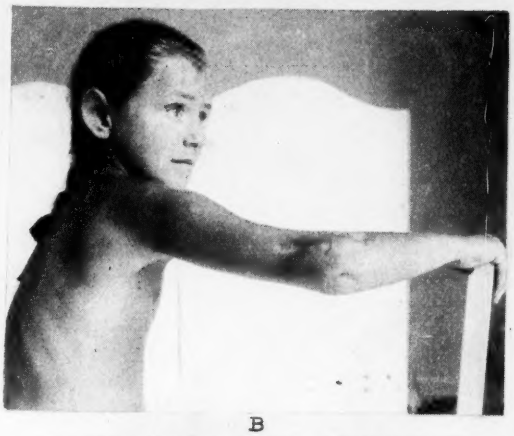
A

B



C

A



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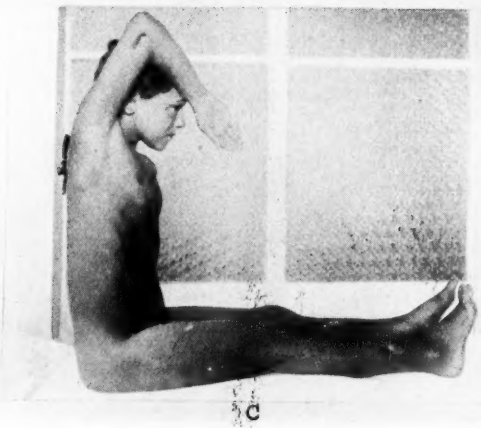


C

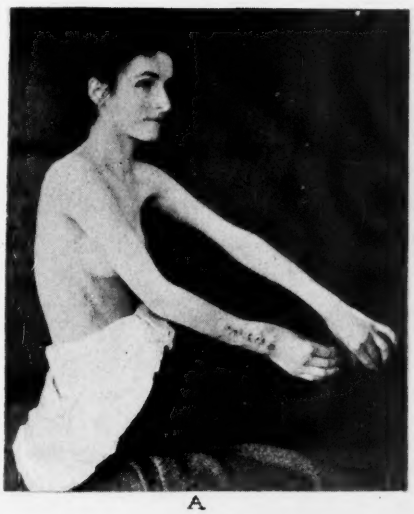
PLATE 3

A. Tuberculous elbow (right) with wounds and numerous fistulae. Ankylosis, fever, mixed infection, general condition very poor.

B. The same cured after 10 months; cicatrization of all the fistulae.

C. The same cured; return of the articular function.

D. The same 15 years later; strong and healthy cook.



A

B

C

PLATE 4

A. Tenovaginitis; tuberculous arthritis of the wrist; peritonitis; renal tuberculosis (nephrectomy); pulmonary tuberculosis of the right apex; slight lupus on the right cheek. General condition very poor.

B. The same one year later.

C. The same 14 years later; a very active nurse. At present (20 years later) keeps in perfect health.

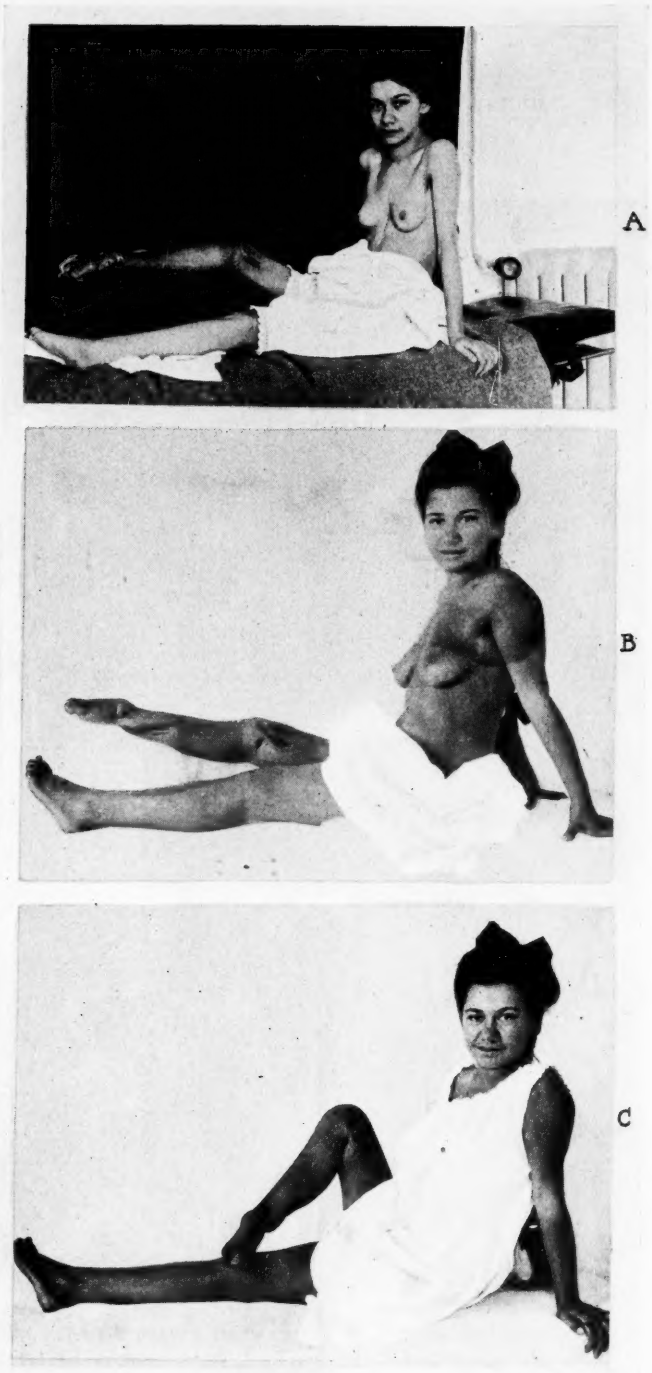


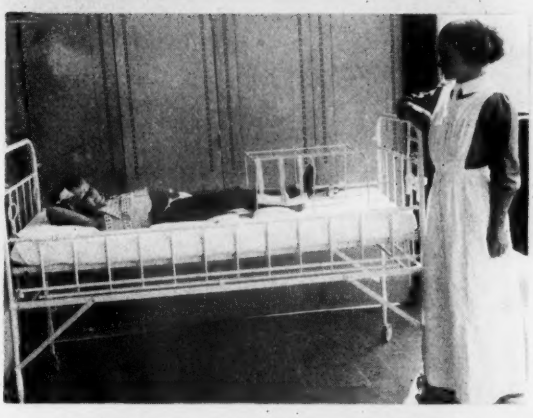
PLATE 5

A. Advanced tuberculosis of the foot, leg and thigh. Operated on five times; 13 fistulae; mixed infection; ankylosis of the foot and knee; general condition very poor; cachexia, high fever, albuminuria.

B. The same 1½ years afterward. Completely cured.

C. The same showing complete return of articular function.

D



E

F

PLATE 5

D. and E. The same; a very active nurse.

F. The same 10 years later. Died in 1918, while in full activity, from an attack of influenza-pneumonia.

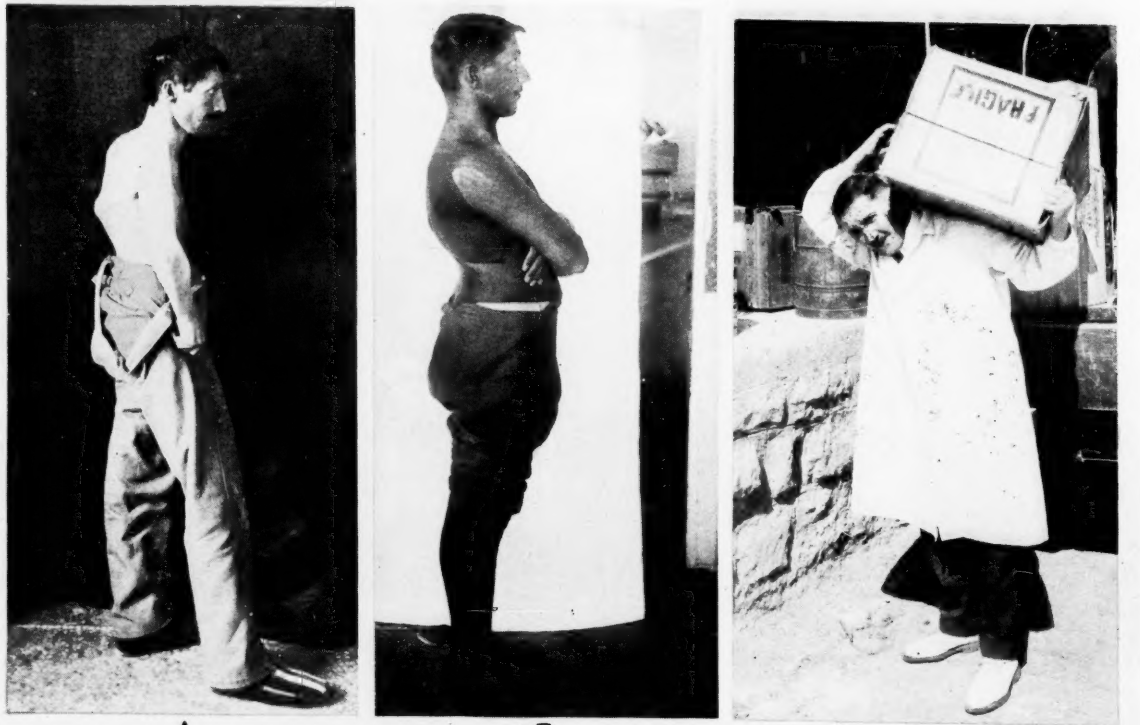


PLATE 6

A. Pott's disease; pulmonary tuberculosis.
B. The same, 15 months later.
C. The same, 18 years later.

A

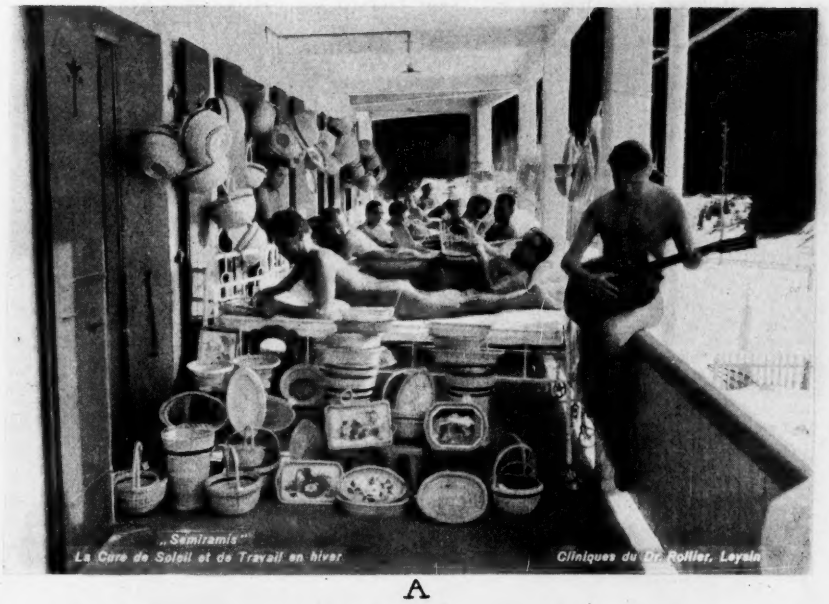
B

C

PLATE 7

A. Pott's disease, with marked curvature and paralysis.
B. The same, cured after 18 months.
C. The same, on her skis during a visit at Leysin for medical control.

C. The same, 18 years later.



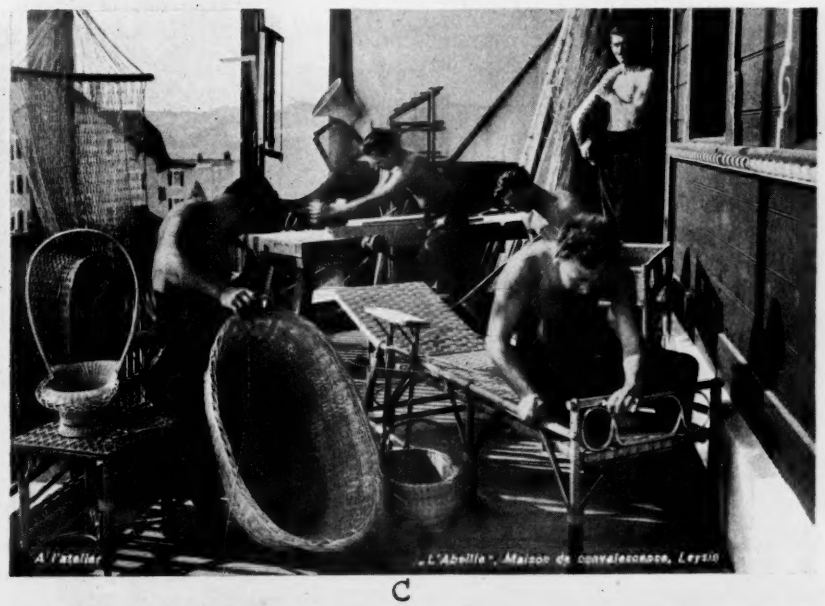
A

B

PLATE 8

THE WORK-CURE

A. Work and sun-cure in one of Dr. Rollier's clinics. (Winter.)
B. Work and sun-cure in one of Dr. Rollier's clinics.



C

D

PLATE 8

THE WORK-CURE

C. House for convalescents, surgical tuberculosis. Workshop in the open air.
D. A patrol of Boy Scouts in one of Dr. Rollier's clinics.

PLATE 8

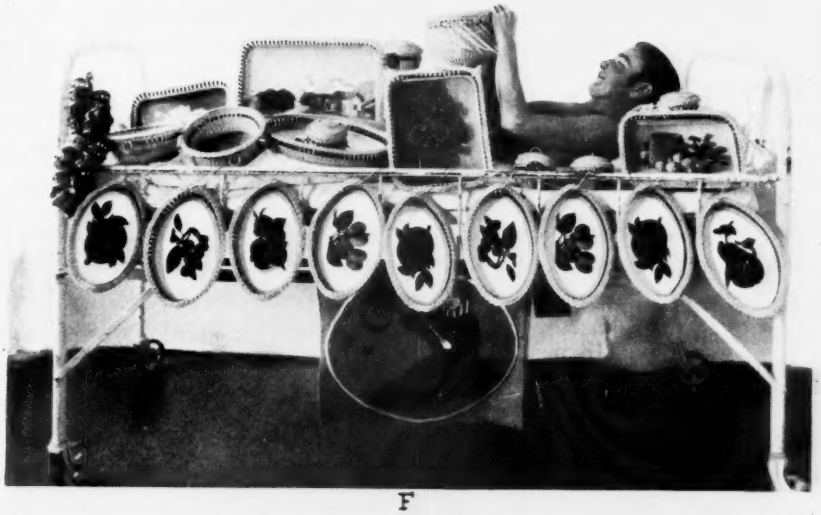
The Work-Cure

E. Sun and work-cure in one of Dr. Rollier's clinics. Bookbinder.

F. Work and sun-cure. A case of Pott's disease and coxalgia in the dorsal position. Weaving baskets, etc.

G. Work and sun-cure. A case of Pott's disease in the ventral position, and a case of adenitis. Making toys.

E



F

G

THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS[1]

GUMERSINDO SAYAGO[2]

The surgical treatment of pulmonary tuberculosis occupies a preëminent place in the therapeutic problem of phthisis. The present fundamental concepts governing the subject are sufficiently rational to warrant its wider diffusion. Belief in the actual surgical methods applied to the treatment of pulmonary tuberculosis is fully justified, and the results obtained in different parts of the world are in accord and attest the value of the therapy.

THE NATURAL CURATIVE PROCESSES AND THEIR VALUE IN SURGICAL TREATMENT

First of all, it is indispensable to speak of the natural processes of healing in pulmonary tuberculosis. Tuberculous foci ulcerate owing to their caseous fusion, and when the defensive processes of the body do not check the invasive march of this destruction the tuberculosis progresses, passing through all the appearances of common phthisis, and terminates the patient's life after a more or less slow course. In other instances this caseous fusion is checked by the formation of new tissue, which represents in itself a natural process of healing. Nevertheless, the diseased body can attain to a like spontaneous healing by other mechanisms without the production of new tissue. In such cases the pulmonary lesions are predominantly exudative and disappear without leaving traces by a mechanism which Jaquerod terms *reabsorption*. This means of natural healing has been adequately demonstrated since patients have been systematically studied by radiology. We do not believe that it is necessary to dwell on this mechanism of natural cure, as it is fully recognized, especially in those clinics devoted to sanatorium treatment. These cases, of course, do not belong to surgery. They are the product, principally, of hygienic treatment precociously applied.

[1] Translated by John Alexander.

[2] Substitute Professor in the Medical Faculty of Córdoba, Argentine Republic, and Physician to the Hospital T. C. Allende.

The new formation of connective tissue can also lead to the natural cure of the tuberculous process, especially in those cases in which its production reaches such proportions as to permit encapsulation of tuberculous foci isolated from the sound portions of the pulmonary parenchyma and, little by little, it invades them completely.

This production of new tissue, which soon acquires the characteristics of adult connective tissue, is the point of departure for anatomical changes of the greatest importance. On cicatrizing, the tuberculous lesions, particularly those of the cavernous type, bring about a reduction in the volume of the diseased lung which, then, causes other anatomical alterations that favor the cicatricial process. We refer to the retraction of all the organs which encompass the diseased lung. Sclerosis of the tuberculous foci compromises the normal static condition of the thoracic wall, of the vertebral column, of the mediastinum and of the diaphragm, all of which may suffer displacement and retraction of variable intensity, that vary intimately with the extent of the cicatricial process and with the age and condition of the subject. If the tuberculous focus is of small extent and undergoes cicatrization, the resulting "compensation" of the body in this process is limited to those parts of the sound pulmonary parenchyma which surround the diseased site. This consists in the production of an alveolar hypertrophy. When, however, cicatricial processes follow upon extensive lesions in the pulmonary parenchyma, especially those of a cavernous type, compensation by neighboring tissues is not sufficient, and other factors must enter, in order to favor the development of the retraction of the diseased lung. It is in these circumstances that we see the appearance of a marked retraction of the hemithorax (more intense at the level of the lesion), at times scoliosis; and the radiograph demonstrates deviation of the mediastinum, considerable cardiac displacement and decided retraction of the diaphragm. The most important of these mechanical alterations is the deviation of the trachea and heart which at times reaches considerable proportions.

These phenomena, however, do not always take place in unison. When tuberculosis occurs at an epoch in life in which the thoracic rigidity is great, the thoracic retraction is but little marked, and under these conditions the only organs which accompany the diseased lung in the direction of cicatricial contraction are those which by virtue of their anatomical constitution are still in condition to support displacement (mediastinum and diaphragm). As is easy to understand, the physiological compensation in such cases is not realized in a manner wholly

favorable to the natural process of cicatrization, and many times, even when the thoracic wall participates, the condition of the lesions prevents realization of healing, in spite of considerable development of fibrous tissue. It is in such conditions that surgical procedures lend their aid, completing the work that the organism has imposed but has not been able to terminate, owing to the impossibility of conquering the rigidity of the thorax.

It is known, nevertheless, that before such anatomical modifications as we have just described occur at the level of the diseased lung, artificial pneumothorax can contribute to the healing of the lesions by immobilizing and compressing the diseased lung. Cure by this therapeutic procedure is not, however, always possible, and then surgery performs its rôle, managing to mobilize those portions of the thoracic wall that still resist the natural process of retraction, in such a way as to create a new conformation, in harmony with the defensive work that is being accomplished in the interior of the diseased lung. By this mobilization, surgery makes of the rigid parts of the thorax "a kind of sculptural work in the living body, an artistic work erected on a pedestal of the most exact knowledge of surgery and of normal and pathological anatomy."

HISTORY

In 1885 were begun the first plastic operations on the thorax applied in the treatment of pulmonary tuberculosis. Truc performed a partial plastic operation, seeking the retraction of a cavity that had previously been opened, and de Cérenville resected the fifth rib in order to obtain retraction of an underlying cavity.

Ideas of Quincke: Such were the first surgical attempts that preceded Quincke, when in 1888 he affirmed as follows:

> In pulmonary abscesses of major volume (only these merit the name of cavities) the adjacent tissue has suffered a callous thickening of great extent and is filled with inflammatory and tuberculous foci and frequently is adherent to the thoracic wall. Simple opening of the abscess is not efficacious because its contents are not under pressure. Persistence of the cavity is due, chiefly, to its being held in a distended condition; it can close only on cessation of this state of tension. Still, when the cavity is encysted, its substitution by a cicatrix, even though this be only partial, constitutes a very appreciable advantage, because not only is a superficial suppurating focus destroyed, reduced or encapsulated, but also—and principally—the permanent foci of colonization of

infectious material which constantly is being renewed. Surgical intervention will be indicated in those cases in which the tuberculous focus (one or several cavities) is circumscribed but in which the rest of the lung is completely or almost completely healthy. In these cases diffuse tuberculosis, which threatens to occur, can perhaps be prevented by partial resection of the upper ribs and the artificial formation of a pulmonary cicatrix.

The ideas of Quincke did not make due progress in spite of the favorable opinion of the Hoffmann clinic.

Spengler and Bier: In 1890 Carl Spengler noted that chronic pulmonary phthisis leads to a lessening in size of the whole lung, this being caused by cicatricial retraction, which in its turn provokes deviation of the heart, mediastinum, etc., and that the only thing that opposes this curative retractile process is the thoracic wall, the inelasticity of which must be offset surgically, so as to favor the natural contractile tendency of the lung by mobilizing the thoracic wall at the level of the diseased site or elsewhere, trying to reduce the volume of the organ by reduction of the size of the thoracic cavity.

Later Quincke insisted on his first ideas, spoke of the rigidity of the superior thoracic strait as favorable to the localization of cavities at the apex, and as a curative procedure spoke in praise of costal resection which would favor the free production of sclerotic tissue.

Bier, applying Quincke's ideas, resected the anterior parts of the second and third ribs for a cavity in the right upper lobe, and a year later resected nine other ribs because of a fresh hemoptysis. The patient, however, succumbed and a necropsy showed that the cavity was well compressed and that the recent accident occurred in a new cavity.

The Ideas of Turban: In 1899 Turban said, "In order to facilitate pulmonary retraction it is not necessary to mobilize the thoracic wall at the diseased site; it suffices that the thoracic resection be made in some other location to benefit the whole lung; resections at the base affect the apex, under good conditions." He counselled costal resections in the lower and external portions of the thorax. In accord with these ideas Turban operated upon four patients, one of whom had a sufficiently good result. He advised intervention in those patients with total integrity of the lung of one side and with extensive lesions in the whole parenchyma of the other side, and yet in whom the destructive foci were not of a grave character.

Landerer's Statistics: In 1901 for the first time Landerer published

statistics upon nine operated cases. The resections employed by Landerer embraced five ribs and in amplitude were greater than the extent of the lesions. So this author, as also those of like surgical intention who preceded him, held the opinion that thoracoplastic operations were indicated only in the stationary or slowly progressive forms, and that acute processes remained at the margin of the field of indications.

If an analytical study be made of the thoracoplasties proposed until the epoch of Landerer, it is seen that all of them had in view only their relation to the natural process of retraction which took place at the level of the pulmonary lesion in those cases which became healed. Those surgeons who resigned themselves to partial resections, mobilizing the thoracic wall at the level of the diseased site or at some distance from it, only facilitated the pulmonary retraction, thereby following the steps already anticipated by Nature and with the same result. Nevertheless it is necessary to note that these surgical methods did not reach the result that was to be hoped in view of their rational conception. Without doubt there existed reasons for this, one of a technical order, the other mechanical. The advent and diffusion of artificial pneumothorax demonstrated that it was necessary to add to the idea of retraction that of repose of the entire diseased lung, since in this way is created a prophylaxis of the healthy parts which, as they remained in activity after partial thoracoplasty, were exposed to the danger of aspirating the septic products of the diseased parts.

The Concept of Brauer and the Method of Forlanini: Doubtless we owe to Brauer the integral conception of the proper manner of procedure. He clearly saw that the method of Forlanini and thoracoplasty lead to the same goal, although by different roads. Also he understood that this goal is fully reached in pneumothorax upon the production, not only of retraction of the diseased site, but also by complete repose of the organ. This being so, pneumothorax stands first in simplicity of technique and in benignity. Because of adhesions pneumothorax is not, however, always realizable, and therefore thoracoplasty must be planned to produce the same results. In order to accomplish this, it was necessary to effect ample thoracoplasties, which would embrace the integrity of the thoracic wall; that is to say, partial thoracoplasties must be abandoned. Such is the admirable concept of Ludolph Brauer, who gave to surgeons the fundamentals of a rational surgical method which soon was put into practice by Friedrich. Their interventions, some of them favorable in outcome, demonstrated that, in common with pneumothorax, these

thoracoplastic operations, which extended to the whole of the thorax, obtained the same benefits,—almost immediate suspension of expectoration and of fever. If the originators of partial thoracoplasties failed because of the insufficiency of their procedure, the procedure of Brauer-Friedrich led to ruin because of its excess; although, according to our understanding, less from this cause than from defective technique, which made of this operation a traumatizing act. Later fitting modifications, which had to do with the magnitude of the resection and its site, as also the extent of each stage of the operation, created a definitive triumph for the general conception of Brauer.

Practice of the ample operations proposed by Brauer demonstrated a series of inconveniences which served to establish a definite difference between the effects of pneumothorax and of these operations. Doubtless the point of difference is in the removal of the bony thoracic wall by thoracoplasty. Without the resistance of the wall, displacement of the mediastinum must be more frequent. This phenomenon is absent in pneumothorax except in those cases in which the intrapleural pressure becomes very high. Large thoracoplasties cause paradoxical respiration, which is responsible for a vicious circle of the air from the operated lung to the healthy lung and vice versa. The differences between the immediate effects of the one and the other method must be considered. It can be said that the interventions that are at present being practised have almost entirely eliminated the dangers.

The method of Forlanini produces brilliant immediate results in suppressing expectoration and toxic symptoms; then cicatrization takes place silently and in the most absolute secrecy of the gaseous atmosphere which envelops the lung. The years pass and the hour for restoring the lung's suppressed activity arrives, and the physician, trusting the evidence of the moment, must face almost blindly the burden of saying whether cicatricial activity has attained its objective. On the other hand, large plastic operations give the same immediate effects; however, in spite of this, the physician must follow step by step the development of his work; he finds that in spite of the absence of expectoration and toxic symptoms the lung gives auscultatory evidences of the disease and that they persist for a long time; they decrease slowly and finally arrive at the desired goal; the cicatricial process has completed its work.

Thoracoplasty of Wilms and Sauerbruch: The inconveniences which have been indicated in the operation of Brauer-Friedrich were later to be avoided by the technique proposed by Sauerbruch. Before he arrived

at it, however, Wilms proposed his columnar resection, which consisted in extirpating short fragments of the first seven ribs in the region of the costal angle. Following the works of Gourdet, who demonstrated with his cadaver experiments that narrowing of the thorax reached its maximum proportions when the costal resections were made in this place, Wilms brought his operation into practice and obtained good pulmonary retraction. In the cases in which the retraction was insufficient he added resection of short fragments of the anterior extremities of the ribs. There is no room for the least doubt that with the technique of Wilms a most desirable perfection has been reached; that is to say, it has made the operative act a perfectly tolerable intervention for the patient. Nevertheless, the proposition of Wilms was incomplete, since it was a partial thoracoplasty which has all the inconveniences we have already mentioned. Also, I must make understood the true operation of Wilms, since, by particular reports from physicians who saw him operate in the year 1912, we may suppose that already in this epoch he had amplified his resections to include the first eleven ribs, thereby avoiding the inconveniences of partial thoracoplasties, which predispose to aspiration in those uninfluenced parts of the lung that remain in full activity.

It is in this stage of the development of the surgical treatment of pulmonary tuberculosis that the operation of Sauerbruch appeared. This surgeon, following the postulates of Brauer and the new orientations of Wilms, amplified the latter's procedure, and practised resection of the first eleven ribs at the site of election (costal angle). His resection, although always embracing all these ribs, was variable in amplitude, depending upon the magnitude of the lesions; in some circumstances he extracted short fragments, in others he took as much as 6 or 7 cm. From what we have just said it follows that the operation of Sauerbruch is, fundamentally, an amplification of that of Wilms and that under these circumstances it should be dedicated, in homage to both, as the thoracoplasty of Wilms-Sauerbruch, a proposition to which we have referred in previous writings and which was taken into consideration by other authors, such as John Alexander.

Before passing to the study of other surgical procedures we must complete our survey with respect to the new technique of thoracoplasty. It has the virtue of giving all the benefits of a general retraction of the diseased lung, without the inconveniences which belong to the thoracoplasty of Brauer-Friedrich which, by suppressing completely the costal wall, predisposes to paradoxical respiration and pendulum movement of

the mediastinum. The modern technique leaves a large part of the wall in contact with the diseased lung, thereby protecting the patient in high degree against these disagreeable phenomena and furthermore maintaining in the operated lung a sort of respiratory function, very restricted, but none the less definite, and sufficient to maintain in it the mechanical conditions favorable to the pulmonary circulation which is useful for the productive cicatricial process.

Partial Thoracoplasties: We believe that we have created the impression of the necessity of abandoning partial plastic operations. But it is important to add that they can still be practised under definite conditions. When after the institution of an artificial pneumothorax, the site in which an important lesion is located remains adherent to the thoracic wall, mobilization can be effected by a partial plasty. Our statistics show an intervention realized under these circumstances and, with this observation as a basis, we think, nevertheless, that partial plasties actually do not give major benefits, since they require maintaining the patient under the influence of repeated pneumothorax with all its inconveniences and possible complications, and, furthermore, partial operation does not succeed in giving a truly useful retraction. Also, this course implies prolonging indefinitely the immediate supervision of the patient, with consequent grievances, all of which could be avoided by proceeding in these cases to a total plasty. This is the criterion which rules in the different surgical centres of Europe and North America, and which our short experience keeps confirming.

Phrenicoexairesis: Phrenicotomy, to which we have already referred, alone remains for our study. The fundamental principles of this operation are already well known. It has spread far in recent times, but too much has been expected of it. The final benefits are, in general, either transitory or indifferent, owing to the fact that paralysis of the diaphragm in itself is incapable of maintaining in an effective way the conditions of repose and retraction which the diseased lung demands for its cure. In common with other authors we have obtained results that have been more or less durable, that have freed the patient from important symptoms, hemoptysis among others, but they have been insufficiently sustained to bring about a cure as a result of phrenicotomy performed alone. From this point of view this operation should not be considered as an independent procedure, but it attains great importance when it is combined with other therapeutic procedures. We shall see later, when we consider the functional conditions that must exist in the lung when a

thoracoplasty is indicated, that phrenicotomy attains great value. Moreover, it has frequently been utilized in combination with the method of Forlanini, particularly in those cases in which the inferior lobe remains distended by adhesions. This procedure has been objected to, on the ground that it is beneficial only when the intrapleural pressure is negative, since only then does there exist the possibility of ascension of the cupola of the diaphragm and, in consequence, a major compression of the lung. However, if the intrapleural pressure be positive (and a positive pressure is necessary in these cases to maintain an efficacious collapse), it is impossible for the diaphragm to ascend; and, on the contrary, it is crowded toward the abdomen, owing to its paralytic atonicity. Nevertheless, if there be adhesions that hold the lower lobe to the diaphragm, provided they are not extensive surface adhesions, it is possible to attain important results, in view of the fact that the atonicity of the muscle facilitates a crowding away of the diaphragm, together with the adherent lung, to the median mediastinal plane. Reventós of Barcelona has recorded interesting observations of this sort. The technique of phrenicotomy has varied recently and now surgeons do not practise simple resection of the nerve because of anatomical reasons (nerve anastomosis), and prefer phrenicoexairesis; that is to say a sort of drawing forth of the nerve. Our own interventions have been undertaken according to this criterion.

PULMONARY PATHOLOGICAL PHYSIOLOGY AND ITS RELATION TO THORACOPLASTY

Before speaking of the indications of thoracoplasty, it is necessary to study the functional condition of the patient intended for operation, and especially the character of the lesions which may exist in the better side or in other organs.

Total thoracoplasty, even when it is realized in two stages, suppresses within a very short time the functional activity still existing in the diseased lung, and consequently demands of the whole body, from the very day following its performance, an increased activity compensatory for this deficit. The compensation must be in proportion to the character of the lesions and to the stage of their evolution. If the case presents lesions of recent formation it is natural that the lung of the opposite side and the heart should not have had time to compensate for the diminished function of the diseased lung. On the contrary, in affections of great extent these inconveniences disappear. Nevertheless, it is not only the

antiquity of the lesion that must be taken into account, but also its extent, in order to be able to evaluate the conditions by which it may have arrived at a state of compensation.

When thoracoplasty is undertaken for lesions that are not extensive, one must consider that retraction of the lung affects not only the diseased portions but also those that are healthy and that, therefore, from the moment of operation, it suppresses the activity of the good part of the pulmonary parenchyma. This is of great concern in the case of an organism as frail as it is in tuberculosis. It is indispensable that this concept be clearly understood, since it is decisive in determining the proper operative conduct; and the surgeon will be obliged, in view of these circumstances, to divide the operation into two parts, so as to arrive gradually at the functional suppression of the diseased lung. For still greater security in such cases a preliminary phrenicoexairesis, which mildly limits the function of the diseased lung, is demanded. These concepts clarify for us some poorly understood observations upon the surgery of pulmonary tuberculosis. In effect, when we operate on patients with limited lesions we can confirm the following very interesting fact: If the lesion be situated in the upper lobe, the first stage of the thoracoplasty (upon the lower ribs), that suppresses the activity of the healthy portions of the lung, results in an alarming postoperative condition, characterized by anxious respiration, tachycardia and cyanosis. But the second stage of the operation, which involves major technical difficulties, passes without inconvenience for the patient; this is simple to understand if one considers that the second stage of the operation brings about a compression of only the diseased portion of the pulmonary parenchyma, the functional value of which is nil.

When the lesions of the lung to be treated are old and, above all, when they have attacked it throughout without leaving any part sound, so to speak, thoracoplasty does not represent for the body in general and, above all, for the sound lung and for the heart, an appreciable functional loss and the complete collapse of the lung passes without major compensatory exigencies. It is precisely under these circumstances, and when the conditions of resistance permit, that thoracoplasty in one stage is advisable.

However, there is an immunobiological factor that must be recorded. It is concerned with the mobilization of toxins which is caused by the operative act. They pass into the general circulation, and the organism experiences the effect, important in some cases, and then the true reaction

manifestations of tuberculin appear, and later there is an action upon latent lesions which, as a result of these toxic crises, may become active. This consideration will perhaps justify operations in many stages (three or more) which, however, cause inconveniences of a mechanical nature, to which we shall refer later when speaking of the results of our experience. Only in rare instances has the immunobiological phenomenon been clearly demonstrated to be present, judging from our own and other authors' observations, and what might be interpreted as a toxemia is in reality merely a simple retention of the exudate from the lesions, due to the difficulty of expectoration during the first two or three postoperative days, since once expectoration is reëstablished all becomes orderly.

We have said that in the patients with extensive lesions the better lung has had time to adapt itself functionally and take the place of the diseased lung. However, in those cases in which thoracoplasty is to be performed and, above all, when the diseased lung presents only limited lesions, one should well assure oneself of the degree to which compensation has taken place. The presence of the sequellae of pleuritis, such as extensive adhesions between the lung and diaphragm, as also chronic or emphysematous bronchial processes, are indications of an excessive functional load which might destroy the equilibrium existing until the time of operation.

Although we shall not consider, in this relation, the questions referring to technique, it is our conception that the problem that concerns itself with the modalities of thoracoplasty is intimately linked with the study that we are making. We have previously stated our opinion with respect to phrenicoexairesis preliminary to thoracoplasty in its relations with the extension of the tuberculous process from the operated lung. We have not, however, referred to the usefulness of this same intervention in those patients whose functional equilibrium is undetermined. So as to make the concept more complete, we say that our expression *undetermined functional equilibrium* refers to the cases in which the specialist harbors doubts as to the supplementary activity that the healthy lung is capable of supporting, not only from the point of view of respiratory function, but also with respect to the degree of tolerance of its lesions which have been inactive. It is in these conditions in which preliminary phrenicoexairesis represents a test operation that the doubtful situation is put to proof without exposing the patient to major danger. If the result of the trial intervention is favorable, surgical treatment may be proceeded with, and a thoracoplasty performed in two stages; if the test is unfavorable, the

indication is that a happy outcome probably can be reached only with difficulty. When there is no doubt as to the capacity of a case with respect to intervention, and when there are extensive lesions which have eliminated function in the diseased lung, the problem of a thoracoplasty in one stage presents itself,—an operation which technically is most brilliant and which has the advantage of reducing the discomforts of the patients to a single surgical act. Actually, the surgical centres at Davos and Munich are using the one-stage operation with greater frequency, and we believe that, when the conditions which we have mentioned are met, this operation is very advantageous, since, in addition to the reasons which we have already given, the resulting pulmonary collapse is particularly excellent. Operations in two stages leave an intermediate zone which escapes the desired retraction, owing to the costal regeneration which occurs between the two stages. In addition to this, we must mention the distention produced at the level of the diseased foci, and very particularly at the level of cavities incompletely influenced by the plasty of the lower ribs. This distention occasions disagreeable congestive phenomena which, under certain circumstances, proceed to hemoptysis. Among our observations there are no cases of hemoptysis, and so our favorable opinion of one-stage operations is based principally on the superior mechanical results and on the excellence of the technique. Nevertheless, these intervening hemoptyses have been reported in an alarming form from some clinics (that of Schreiber, among others).

INDICATIONS FOR THORACOPLASTY

In previous publications we have said that if we were to recognize the opinion of Brauer with respect to the indications for thoracoplasty, we would affirm that they were the same as for artificial pneumothorax and that the essential difference between the two methods depends upon the fact that thoracoplasty is intended uniquely for those cases in which pneumothorax is not practicable on account of the presence of a pleural symphysis. This, as a general concept, is indisputable. It is necessary, however, to analyze further the concomitant circumstances which refer principally to the following two points: (1) failure of other treatment and (2) the nature of the lesion. Once the unilaterality of the affection is established and also the impossibility of applying pneumothorax, we must consider and make certain that our patient has no chance of cure by other less dangerous therapeutic measures, for it must never be forgotten that one may speak of surgical therapy only when conserva-

tive procedures have completely failed. From this it follows that the physician, who assumes the responsibility for determining the form of treatment, is under obligation to have first made a prolonged clinical observation of the patient and to have arrived at the conviction that the natural processes of healing have attained their maximum benefit and that it is impossible to hope for more from them. Such is our own practice, and in spite of the enthusiasm with which we have defended the surgical treatment of pulmonary tuberculosis during the past six years, we have never transgressed this law. The nature of the lesion to be treated requires meticulous attention, as does also the duration of its evolution. Recent processes, even when pneumothorax is not realizable, almost always are unsuited for the surgical method, for reasons which we shall give in another place, and surgery is also unsuited for those lesions of brief evolution which have not had time to prepare the local reaction of defense which assures spontaneous cure in the chronic forms.

NATURE OF THE LESION

The nature of the lesion must be well discussed, because upon it depends the result of treatment. Statistical results permit the affirmation that the majority of operative failures concern those cases with predominantly exudative lesions. This is not strange if one considers that these patients have a limited reaction capacity and that in them the natural processes of healing scarcely have been initiated. One of our observations refers to an exudative lesion in the upper lobe in a patient, who, during the course of a therapeutic pneumothorax, developed an effusion which provoked a pleural symphysis. In spite of this the result was brilliant, perhaps because of the previous favorable influence of the pneumothorax and the slight extension of the focus. When exudative processes are of a pneumonic or diffuse bronchopneumonic nature, the contraindication is formal, and the surgical act will only serve to aggravate the precarious condition of the patient. On the other hand, patients with predominantly productive lesions, with an intense development of connective tissue, and with considerable pleural symphysis, —cases which already have given manifestations of retraction, deviation of the internal organs and deformity of the thoracic wall,— come fully within operative indications. When a patient, under these conditions and with an already old disease, must be treated, we ask ourselves whether or not it is necessary to attempt pneumothorax. The authors who have occupied themselves with this question consider it useless because the existing pleural

symphysis, or at least the extensive adhesions, would detract from the efficacy of the treatment. Still, in such cases, even in patients with lesions of six years' evolution, it has been possible for us to realize an efficacious pneumothorax. In one of our cases an extrapleural thoracoplasty was performed without first attempting pneumothorax, in order to treat an extensive process with intense fibrotic reaction, accompanied by deviation of the internal organs and retraction of the thoracic wall. Our having failed first to try pneumothorax in this case was not due to the supposition of extensive adhesions, which certainly existed, but to the very nature of the process. Benefit from this therapeutic method would require a prolonged treatment of several years that was not compatible with the social conditions of the patient, which required treatment of short duration. Under similar circumstances Staub Heinrich decided on immediate thoracoplasty. In our opinion, however, we consider it prudent, except under the conditions just pointed out, previously to attempt artificial pneumothorax.

THE UNILATERALITY OF THE LESION

As with the method of Forlanini, so with thoracoplasty, the pulmonary processes must be unilateral, but the margin of tolerance in the case of thoracoplasty is most restricted. This is clear when one considers that, when contralateral lesions enter into activity, pneumothorax may be abandoned, but when a thoracoplasty has been performed this is impossible. As we have said before, the proper patients for operation are, in general, those with old tuberculosis. An anatomical unilaterality of the lesions is difficult to find and a clinical unilaterality is rare. In a majority of the cases we must intervene in spite of the bilaterality, and definitely conform to the requirement that the lesions of the healthy side be inactive. This is not meant to imply that we must always necessarily think only of the inactivity of lesions. Inactive lesions, when they are extensive, greatly diminish the functional adaptability of the supposedly healthy lung. Consequently, we would say that small fibrotic lesions, or those that have not extended far, or those that have given repeated proof of their clinical inactivity, do not represent contraindications. What has just been said does not apply to exudative lesions, and very especially when they are situated in the hilar region, since at the least functional effort of the lung they become active. On the other hand, one may be somewhat tolerant with small exudative foci that are demonstrable only by the radiograph. Gravesen (1), in a recent publication, is optimistic

with regard to such exudative lesions in the better lung, and believes that the curative action of sanocrysin is capable of a decided influence on them, thereby enlarging the field of indications for the surgical method. In our short experience with chemotherapy, our observations agree with the opinions of Gravesen.

LESIONS OF OTHER ORGANS

Tuberculosis of other organs must be taken into consideration and represents a formal contraindication when it is predominant in the clinical picture, either because of its acute character or the degree of its extension. Under other conditions, not only do such lesions not become aggravated, but they improve as surgical healing takes place in the diseased lung.

Other nonspecific lesions prevent realization of the surgical methods, particularly those that affect the kidney (sclerosis and amyloidosis), and those that cause marked hepatic insufficiency. Only those diabetic patients with phases of prolonged remission may be subjected to surgical treatment. Patients in a precarious general condition, those with positive diazo reaction, and those who suffer from myocarditis or valvular lesions, except in the case of very good compensation, must be counted among the contraindications.

Extremes of age prevent surgery. Patients less than twelve years of age and those more than fifty should not be operated upon. One of our operated patients of thirteen, who had admirably tolerated a phrenicotomy, died from cardiac insufficiency after resection of three ribs, with which operation we initiated an extrapleural thoracoplasty.

CLINICAL SUGGESTIONS OF TECHNICAL UTILITY

The dangers of extrapleural thoracoplasty have appreciably diminished. Undoubted contributions to this improvement are the perfection attained by technique, additional preoperative preparation and, above all, the postoperative care.

The modalities of the surgical act influence the results, and therefore an exact clinical knowledge of the condition of the lung is necessary. The costal resection should be in accord with the nature of the lesion and with the condition of the mediastinum. If the hemithorax is considerably retracted, and cavernous processes are implicated in a good peripheral fibrotic reaction, the pieces of the ribs to be resected should be short,—

not more than 10 cm.,—as this is enough to exaggerate the degree of retraction which already is advanced. On the other hand, in those cases in which the retraction of the costal wall is not intense, even if it is so in the internal organs, particularly the mediastinum, and when the cavities have thin walls with little connective tissue and are highly situated and in the neighborhood of the vertebral column, then the costal resections must be ample if one wishes decidedly to influence the lesions, which is essential because the result of the plasty depends on the perfect apposition of the walls of those cavities, in which one cannot count upon spontaneous cicatrization as one may in the preceding group. The greater the resection the better, especially when it approximates the subscapular resection of Brauer. In order to accept this dictum, one must assure oneself of the condition of resistance of the mediastinum, because when this is somewhat weak extensive removal of ribs leads to dangerous displacement. When one has decided to make an extensive resection it is best to perform the operation in two parts, and to make an orthopedic appliance, which, in part, takes the place of the resistance of the thoracic wall.

Upon the situation of the cavity depends, as we have already said, the extensiveness of each operative act, when one uses two stages, because of the great utility of embracing in the resection the entire height of the cavernous lesion, so as to prevent the phenomena of stretching, which have such great influence in the production of congestion or of hemoptyses intervening between the two stages.

There are certain patients with old productive lesions, bearers of cavities with strong pericavernous cirrhosis which maintains their walls in a rigid condition. In these patients it may be observed that apposition of the walls of the cavity is not accomplished in spite of the thoracoplasty. It has been counselled to overcome this inconvenience by performing an anterior costal resection, which augments still more the degree of the pulmonary retraction. The few cases which we have had the opportunity to see treated in this way in the clinics of Key and of Sauerbruch have not convinced us of the utility of the method, and we believe that, still under these circumstances, an extrapleural pneumolysis with filling will also be inefficacious because the difficulty to be overcome, —the rigidity of the cavity,—is almost incapable of solution. When supplementary anterior plasties are followed by favorable results, this is due, almost always, to the fact that the posterior plasty was inefficacious on account of the high, juxtavertebral position of the cavity.

From what we have just said it is seen with how great reason we affirmed the necessity of an exact clinical knowledge of the lung intended for treatment, so that adequate modalities may be given to the intervention for its happy result.

ASPIRATION PNEUMONIA

We believe that, in the actual state of our technical knowledge, mechanical accidents (especially mediastinal displacement) can be attenuated or avoided in almost all cases; but there exist other dangerous accidents, such as the pneumonia of aspiration. Following thoracoplasty there is sometimes observed in the healthy lung, and at times in the operated side, an aspiration of the septic products which originated in the focus of disease and which consequently lead to a pneumonia that habitually is fatal. Since the time of Wilms, when resection of the first seven ribs was performed, it has been noted that pneumonia of the base was a most terrible and frequent complication. It was then thought that as the collapse was brought about at the level of the superior portions of the lung, the base, by continuing to function, remained capable of aspirating the septic products of the upper lobe. For this reason it has remained established that in thoracoplasties of two or more stages, the lower ribs are the ones that must first be resected, so as to avoid the possibility of so disagreeable a complication. In spite of the contrary opinions of John Alexander as to the mechanism of the pneumonia of aspiration, we believe that the standards of the clinic at Munich should be respected and, when operations in two stages are to be considered, a beginning should always be made with the lower portions of the thorax. Alexander proposes a preliminary phrenicoexairesis followed by an upper thoracoplasty, for the reason that he supposes that in the pneumonia of aspiration the difficulties of expectorating and of coughing, which the patient experiences, have a greater influence than the aspiration action of the lower lobe, which may be suppressed by paralysis of the diaphragm, this not making cough and expectoration more difficult, but, on the contrary, easier. In a case of aspiration pneumonia which appears in our statistics, the complication appeared after the second stage and in the lower lobe of the operated side; the patient recovered in spite of the complication which so seriously menaced his life. In these cases Alexander supposes that, when it comes time for the second stage of the plasty, the base has already acquired sufficient functional activity to stop septic

production;[3] in our case, however, such a supposition is not exact, as an effective phrenicoexairesis had been performed before the first stage.

Under other circumstances, especially following interventions in one stage, pneumonia occurs on the side of the healthy lung, which receives the secretions expressed from the lung that has been flattened rapidly. In one case of pneumonia of the healthy side, which is included among our cases, the complication occurred after complete operation at one sitting in a patient who had a large cavity and very abundant sputum. Nevertheless, the danger of aspiration pneumonia in these cases of operation at one sitting can be greatly reduced if only patients with little sputum are chosen and, above all, patients who have thoroughly emptied their lungs of secretion the morning of operation. Also, it is of value to aid the patient during coughing after operation by using adequate compression with the hands upon the operated side with each coughing effort.

CARDIAC INSUFFICIENCY

Finally, cardiac insufficiency places the life of the operated patients in peril, especially when the intervention has been on the left side. This is because of the mechanical influence upon the heart, or it is the result of operative shock. After having seen such brilliant surgeons as Schreiber and Sauerbruch operate at Davos and at Munich, we believe that the great tolerance of their patients to operations, even those performed in one stage, depends upon two factors, namely, preoperative preparation and intelligent postoperative care; to these we would add the speed and skill with which the operations are performed and the favorable hygienic conditions under which the patients are kept, especially at Davos.

RESULTS

The operative results of the Munich Clinic, reported in the monograph of Brunner and Baer in 1926, include a total of 646 cases with 159 cures (24 per cent) and 115 improvements without tubercle bacilli and with capacity to work (17.8 per cent). The total of these two groups of favorable cases is 42.4 per cent. The mortality, except for the first four weeks after operation, was 86 cases (13.3 per cent); after the second month until 11 years, 108 deaths (16.7 per cent), all from progression of tuberculosis in the originally healthy lung. Besides, there are 27 cases

[3] The sense of this passage is not clear to the translator.

which were not influenced by the treatment or are worse (4.2 per cent), and 38 patients who have not been heard from (5.9 per cent).

The statistics which Professor W. Denk of Vienna has been good enough to send to us include, among 27 cases with productive lesions, 37 per cent of cures, and 37 per cent of improvements without tubercle bacilli and with capacity to work. There was a 7.4 per cent mortality, 7.4 per cent of slight improvement, and 11.1 per cent in which the tuberculosis continued to progress. Taking the first two groups together, there are 74 per cent of favorable results. Among 9 cases with exudative tuberculosis, none was cured, two were improved, in two the results were indifferent, and five died.

The statistics of Gravesen (2) show, among 131 operated cases, 47.5 per cent of favorable results, 19.2 per cent improvements, 25.8 per cent indifferent results and a 7.5 per cent mortality. The results in 109 cases from one to seven years after operation are as follows: fit for work, 43.1 per cent; not fit for work, 13.8 per cent; dead from progression of tuberculosis, including the operative deaths, 40.4 per cent; dead from other causes, 1.8 per cent; not heard from, 0.9 per cent.

The statistics of Jacobaeus and Key (3) of Stockholm are as follows: among 60 patients operated on between the years 1915 and 1922 there were 25 per cent of cures, 31.1 per cent of great improvements, 8.3 per cent of indifferent results, 8.3 per cent of operative deaths, and 26.6 per cent of deaths from progression of the disease and from other causes.

The statistics of Bérard of Lyons, which were reported by Guilleminet and Madinier (4), include 14 cures and 14 improvements, but no mention is made of the mortality.

Our own statistics include 14 typical thoracoplasties, among which three were operated on in one stage and 11 in two stages of which nine had a previous phrenicoexairesis. The results follow:

Operative results after from one to five years

NUMBER OF CASES OPERATED ON	CURES; FIT AND WITHOUT TUBERCLE BACILLI	IMPROVEMENTS	DEATHS	
			Operative	Progression of tuberculosis and other causes
14	4 28.5%	5 35.7%	2 14.2%	3 21.4%

Among the cases listed as improvements we believe that at least three will attain a cure, in view of the great benefit that they have received

from the operation. Under these conditions our favorable results will total 50 per cent. As a result of thoracoplasty we have had only one death from caseous pneumonia; this was twenty days after operation in a patient operated on in one stage. Our other operative death was after a complementary extrapleural pneumolysis with filling, but fourteen months after the thoracoplasty; the patient died from an aspiration pneumonia of the healthy side. One of the three remaining deaths was due to hemoptysis three months after operation, one to uremia and one to progression of tuberculosis.

We have also to report a series of atypical operations (one of them combined with pneumothorax) and other surgical interventions. The total number of these cases is 7. There were five partial thoracoplasties, with one operative death and three deaths due to progression of the tuberculous affection; the result in one case is unknown. One case of phrenicoexairesis was improved, as was one of extrapleural pneumolysis with filling.

As may be seen, the result of our partial operations was disastrous. It should, however, be stated that all of these patients suffered from very grave forms of tuberculosis, one of them from a pulmonary perforation. The phrenicoexairesis and the pneumolysis with filling alone gave more or less lasting improvements.

We believe that in time our statistical results will improve because of the confidence that is had in the surgical methods. This confidence we feel is justified. We base this opinion on our brief experience and on our observations made in other clinics, such as that at Davos, where one cannot help but admire with emotion the brilliant results from twelve years of work, attested by the solid cures which many patients have maintained during that entire time. The confidence of the sanatorium physician will pave the way for precocious intervention in properly selected patients and, on the other hand, will warn against expecting conditions of extreme gravity to yield to surgical treatment.

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FACTORS INFLUENCING THE EARLY MORTALITY FOLLOWING EXTRAPLEURAL THORACOPLASTY[1]

EDWARD ARCHIBALD

Ever since the paper of Sauerbruch and Elving in 1913, the operation of extrapleural thoracoplasty for unilateral pulmonary tuberculosis has been accepted by connoisseurs in this branch of medicine as worthy to take its place among the classical surgical procedures, and all thinking surgeons agree in giving credit for this to Professor Sauerbruch. We do not forget the fundamental work of Quincke, Spengler, Turban, and Brauer and Friedrich, above all of Brauer. It was Brauer who first laid down, on a scientific basis, the principle of the ideal operation, that is, total rib-removal on one side. But the ideal is dangerous; and this particular ideal, carried out in practice, was no exception to that rule. To Sauerbruch belongs the credit of seasoning it with the salt of physiological common sense and clinical experience. The Brauer-Friedrich operative mortality of 28 per cent becomes the Sauerbruch mortality of 13.6 per cent. It is now the task of all of us, altering the plan in detail, to make it still lower.

When your President did me the honor of inviting me to give a paper at this meeting, I felt that the most immediately important aspect of this whole question, now that so many are taking it up, was that of operative mortality. For indeed, if the procedure is to become in this country a recognized classical operation, which those who know are convinced it deserves to become, then it is of the utmost importance that there should occur as few deaths resulting directly from the operation as is humanly possible. In the face of a high operative mortality the arguments of the specialist in favor of the operation meet an opposition on the part of the patient and the patient's physician which is not unreasonable. It behooves us, therefore, to make a close study of the causes of death ascribable to the operation, in the hope of being able to diminish the number of early fatalities. In what follows I propose to examine

[1] Presented before the Clinical Section at the twenty-second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 4, 1926.

seriatim the various causes of death after operation. For that purpose I have gone over my own series of cases, I have read the published reports, and I have made personal inquiries of a number of American surgeons. I shall venture to expose in some detail the principles upon which I base my own practice, and I shall not hestitate to express some disagreement with the practice of others, for only in this way, the way of lively discussion, can we hope to improve practice.

Before proceeding to detail it is necessary to delimit the subject. I am considering at this time only the operation of posterior extrapleural thoracoplasty, either by the Sauerbruch paravertebral method, or the Brauer subscapular paravertebral method. I exclude expressly such ancillary operations as phrenicotomy, apicolysis, the cutting of intrapleural adhesions, intrapleural or extrapleural pneumolysis, and pneumolysis with *Plombierung* of paraffin, fat or muscle. The Sauerbruch and the Brauer methods differ essentially only in the length of rib resected, but either of them is a standard procedure and is the only procedure to be considered in the vast majority of cases. When it has failed to relieve or cure the ordinary case of advanced pulmonary tuberculosis, it is not often that secondary or complementary operations do much good. I leave out of consideration, also, the cases of pyopneumothorax, due to mixed infection, frequently with a bronchopleural fistula, in which the condition is more or less desperate; but I include cases of pneumothorax complicated by fluid, in which the tubercle bacillus alone may or may not be found, but in which a bronchopleural fistula has not occurred. These, in my experience, so far as the danger of the operation and the results following operation are concerned, can be considered as almost equivalent to the ordinary case.

Under these limitations the count of my own series of cases amounts to ninety. In passing, I might mention that the rest of my personal experience comprises 10 cases of pyopneumothorax of bad type, 5 cases of open intrapleural cutting of adhesions, which were restricting an otherwise good pneumothorax, and 3 cases of apicolysis with muscle filling, as a late secondary operation—a total of 108 cases in which major operations under general anaesthesia were performed.

If we now take in their order the causes of operative death, as generally recognized, we may begin with that which is called *operative shock*, whereby the patient, within one or two days after operation, dies with symptoms of collapse. The idea is that of shock in the generally accepted sense, due to the operative act *per se*. It is extremely difficult to dis-

tinguish from *cardiac failure*, which is usually accompanied by, or caused by paradoxical respiration, from anaesthetic poisoning, and from acute intoxication (protein?), derived from tuberculous tissue. My impression is that death is often due to a combination of all these factors. While death from pure shock sometimes occurs, to judge from the description of postoperative conditions in various reports, I have come to believe that such fatalities are observed chiefly as a direct result of the one-stage operation in patients who are poor risks. In the two-stage operation there has been, so far as I could judge, very little pure operative shock in my own cases. The figures of Alexander, based upon analysis of the entire literature, that is, a series of 1,159 cases, are approximately 1.5 per cent of all the cases operated upon, and in Sauerbruch's figures it is a little under 1 per cent (Brunner).

In my own series of slightly over 100 cases, including the pyopneumothorax group, and about 200 distinct operations, I have not had to deplore this accident. It is unfortunate that, apart from Brunner's list of carefully and fully reported cases, numbering 117, there have been published very few articles in which the facts of each case are fully set forth so that the independent reader might form his own judgment as to the cause of death. Usually a death in the first two or three days is set down in a general way as due to "operative shock and heart failure."

In a few cases the author has decided definitely that the death was due to novocaine poisoning. Gravesen reports two such in a total of 97 cases, while from American operators (personal communication) two more are reported. Altogether, I find 7 novocaine deaths reported. Concerning these last I would immediately express my own opinion, which is, that such novocaine deaths are to be laid at the door of the generally accepted principle that the operation should be done under local anaesthesia. Yielding to this supposed necessity, undue amounts of novocaine have been injected, as high even as 300 cc. of a 0.5 per cent, plus 50 to 75 cc. of 1 per cent solution (Bull). Such amounts are within the danger limit. They may be necessary for anaesthesia if one is to exclude all general anaesthetics, but the practice is responsible for unnecessary deaths. In my own work I employ exclusively gas-oxygen, with 0.5 per cent novocaine for the skin, and 1 per cent for the intercostal nerves, the latter being injected after the ribs are exposed. The ordinary amount used is between 20 and 30 cc. for the skin, and from 10 to 15 cc. for the intercostal nerves, and the addition of adrenalin is avoided. Not infrequently I have dispensed with all local anaesthesia for the nerves,

finding the gas anaesthesia sufficient. With these amounts I have observed no instance in which the early postoperative symptoms could be credited exclusively to novocaine. Nevertheless I am gradually tending to limit its use to a few cubic centimetres for the skin anaesthesia. If one will insist on using large amounts, a test dose of novocaine (Saugman) on the day previous to operation should be given, in order to discover a possible idiosyncrasy for novocaine.

The ill effects of too extensive a removal of ribs over a lung, which has not been rendered stiff by pleural thickening, or by infiltrating and fibrosing disease in the lung itself, and in the presence of an unstabilized mediastinum, are very evident. They result in a marked tachycardia and an increased respiratory rate, both of which depend upon the changed conditions of physiological respiration. The increase in the rate of the heart, as seen often after a first-stage removal of the lower ribs, when there is no likelihood of tuberculoprotein intoxication, must be purely mechanical in origin. The rapidity of the pulse often lasts for two weeks, or indeed much longer, before the chest becomes sufficiently stabilized to offset the mechanical change in the thoracic skeleton. All this time the temperature may remain practically normal, yet the strain on the heart muscle involved in this tachycardia cannot be underestimated. When to this is added, as the result of the necessary manipulation of the diseased lung, particularly during the removal of the upper ribs over cavities, followed by a separation of the lung from under the rib-stumps, a serious intoxication with tuberculoprotein (in the fact of which I firmly believe), it is easy to understand that the weaker patients may succumb. Such deaths in the first two or three days are ordinarily put down as due to collapse, shock, or cardiac failure. It is a composite picture, and I think death is due to a combination of these factors. Out of Brunner's 13 cases of early mortality he had one such death. In Stoecklin's 100 cases there were 4 on the first day, and 6 from the second day to the seventh day. In the American and Canadian statistics, including 270 cases (personal communications), there were 20 deaths in the first three days, the usual cause given being cardiac failure from paradoxical respiration and myocarditis.

Concerning such deaths, one can only say that they are best avoided by not doing too much at one time, both as to the number and the length of ribs to be resected. I have made it a rule never to operate in one stage, a rule which I have broken only in two cases (of whom one died on the eighth day). Statistics are accumulating as to the very much

greater danger of the one-stage than of the two-stage operation, and for myself I am not prepared to accept the extra risk involved in the one-stage operation, no matter how favorable the patient's condition may be. More than this, I am inclined to extend the operation into three stages in any patient whose general resistance seems to be doubtful. Hedblom (personal communication) reports 15 cases done in three or more stages without a death. It is true that such a method does not ordinarily result in as perfect a collapse of the chest-wall as when the operation is done in one or two stages, but that is of less importance than the preservation of life.

As to the length of rib to be resected, I think there has been too much made by some (Brauer, Bull, Stoecklin) of the necessity of excising a considerable length of the rib in order to get a better collapse. In general, the good effect of thoracoplasty is to be ascribed much more to the functional rest given the lung than to the compression of the lung, and the difference in the ultimate good results, as between those who make a long resection and, say, Sauerbruch, who limits the resection to from 4 to 8 cm., is insufficient to compensate for the greater immediate danger to life. It seems to me certain that the degree of mediastinal flapping and paradoxical respiration is more or less directly proportional to the amount of rib removed, and that Brauer's subscapular paravertebral method is more dangerous to life than Sauerbruch's paravertebral resection. It is, therefore, impossible to make any definite rule as to the length of rib to be resected. This must depend upon due observation of the patient's general condition during the operation, as to rate and volume of pulse, and upon the evidence of inspiratory falling in of the lung as observed during the progress of rib removal. If, for instance, after I have removed 10 to 15 cm. of the 10th, 9th and 8th ribs, I find an unsupported lung falling in markedly, I then resect much shorter lengths of the 7th and 6th ribs, and stop there, or finish by removing 6 to 8 cm. of the 11th rib. A reasonable degree of paradoxical respiration over the lower lobe is then usually well borne; and, if the chest has become stabilized in the next two or three weeks, one is able, with much greater safety, to remove 8 to 15 cm. of the upper five ribs at the second stage. In patients who are not very resistant, and whose general condition is not favorable, one resects much less than this, following Sauerbruch. The early mortality of Bull, who resects as much as 180 cm. of rib, is higher than that of Sauerbruch who resects much less.

One of the rules of the operation of thoracoplasty that has been hitherto

considered as most soundly established has been that laid down by Sauerbruch, that if the operation is to be done in two stages the lower ribs should be first resected, in order to compress the lower lobe, set it at rest, diminish or abolish its respiratory movement, and in that way prevent the aspiration of infected material from the uncompressed upper lobe. In Sauerbruch's early experience there were four patients (five operations) in whom the ribs over the upper lobe were first resected, of whom two, as a result, developed an acute tuberculous pneumonia, or bronchopneumonia, of the lower lobe. One died in three months and one in eight months. As a result of this experience he laid down the rule just mentioned.

During the last ten years many modifications of technique and general procedure have been proposed, designed to meet particular conditions, but of these the most revolutionary has been that suggested by Alexander, who, less than two years ago, as the result of a most exhaustive study of the literature, came to the conclusion that the incidence of postoperative tuberculous infection of sound or relatively sound portions of the lung, following the standard thoracoplasty as done according to Sauerbruch's rule, was greater than it should be. He refers particularly to the statistics published by Stoecklin, from Schreiber's clinic at Davos, and by Brunner, from Sauerbruch's clinic at Munich, these being the only large series of cases in which sufficient details are given for the study of the causes of death. His point is that in order to form an independent judgment of the cause of death, the full details of the case-report are necessary. He points out that of 24 deaths, more or less directly connected with the operation, as reported by Stoecklin, 6, or 25 per cent, were due to aspiration pneumonia, while, of Brunner's series of 99 posterior thoracoplasties, tuberculous pneumonia was either the sole cause or one of the gravest of several causes of death shortly following operation in 10, which is 83 per cent of the 12 cases. Too little attention, he thought, had been paid to the cause and prevention of pneumonia following thoracoplasty.

As a result of his study of the latter, he came to the general conclusion that the removal of the lower ribs first constituted a surgical sequence which favored the development of pneumonia. In Brunner's 99 cases, fatal pneumonia occurred five times in the lower lobe of the operated side, and seven times in the lung of the good side, while in Stoecklin's 96 cases it occurred twice on the operated side and four times on the good side. Alexander states that this same complication has frequently been

reported by other surgeons. After a careful study of the whole literature, he failed to find evidence to support Sauerbruch's fear of primary upper-lung compression as the cause of postoperative pneumonia. "Relatively few cases of pneumonia have been reported (in primary upper-rib resection), whereas reports of pneumonia following primary resection of the lower ribs are relatively frequent." If this difference of results is a fact, it cannot, as he points out, be due to any difference in the resistance of the patient nor to the anaesthesia (usually local), nor to operative shock nor to increased respiratory activity of the uncompressed lung (pneumonia is extremely rare after total compression of one lung by artificial pneumothorax), nor to excessive autointoxication. In short, he believes it to be due to an impairment of the expectorating power, resulting from a resection of the lower ribs. Primary lower-rib resection interferes with the work of the chest muscles, and especially the abdominal muscles, which are the prime factors in efficient coughing and expectoration. This results in stagnation of tuberculous sputum in the lower lobes. Moreover, the breathing lung of the unoperated side is more liable than the compressed lung to aspirate infected secretion, which accounts for the higher incidence of pneumonia in the uncollapsed lung.

Alexander points out also that pneumonia occurs far more frequently after the first stage of lower-rib resection than after the second stage. "Among the 16 cases of postoperative pneumonia reported by Brunner and Stoecklin, 12 occurred after resections that were confined to the lower chest, where the tuberculous lesions were usually absent or few in number." There were 3 additional cases following a one-stage operation, so that 15 of the 16 cases of pneumonia occurred after operations that included the lower ribs. Only one case followed a second-stage thoracoplasty of the upper ribs, several weeks after a first stage on the lower ribs. Alexander also points out the analogy of the occurrence of pneumonia after operation on the upper abdomen, and the analogy of pneumonia following tuberculous haemoptysis when the patient's cough is subdued by opiates. He also quotes Sergent and Ameuille, who demonstrated that bronchial emboli aspirated to the base of the lung are easily expelled by coughing, from which follows the conclusion that the development of pulmonary infection does not depend so much upon the mere contact of infectious material with the lung as upon the duration of that contact.

As the result of these considerations Alexander proposes a change in procedure. The ideal operation, he says, would be one which would

keep the lower lobe from aspirating infected secretion at the time the upper-lobe lesions were emptied of their infectious contents and yet would not impair the function of expectoration, and, at the same time, one which would rest and relax the entire lung sufficiently to heal the tuberculosis. In this sense he proposes a primary phrenicotomy, followed in several weeks by a thoracoplasty of the upper seven ribs. He assumes that the phrenicotomy excludes the lower lobe from respiratory function almost to as great an extent as is done by a first-stage thoracoplasty, without impairing the power of cough and the ease of expectoration; and that, therefore, the danger of aspiration is largely eliminated. As the result of experience, it is found that cough and expectoration are easier after phrenicotomy than before, although the tidal air in the lung is lessened. This, Alexander thinks, is because the abdominal muscles act more strongly through an atonic diaphragm in coughing. Inasmuch as the lower lobe is usually but little diseased, he believes that the above-mentioned procedure would often suffice without the addition of a lower-lobe thoracoplasty; but, if the lower lobe is more than a little affected, he would advise a second-stage thoracoplasty upon the lower ribs, from three to six weeks after the operation on the upper ribs.

I have set forth Alexander's arguments in detail because his proposal represents a serious change in practice, and also because I feel obliged to disagree with them, at least in part. The chief force in Alexander's argument depends upon the proof of an undue mortality rate from postoperative pneumonia under the Sauerbruch procedure of resecting the lower ribs first. One must first point out that the pneumonia, or bronchopneumonia, reported as the cause of death from the end of the first week on through several months, is usually a tuberculous process and not an ordinary aspiration pneumonia such as is seen in general operations after a general anaesthetic, due presumably to the aspiration of infected mouth secretions. Being tuberculous, the question immediately arises as to what proportion of these may be due to an activation and lymphatic spread of already present disease, and what to a direct aspiration of tuberculous pus, presumably emptied from cavities in the upper lobe. Alexander's argument can obviously apply only to the latter circumstances, inasmuch as activation of preëxistent disease may be caused by the general lowering of the patient's resistance, resulting from the operative act. Nor can one agree with his contention that a phrenicotomy is as efficient in abolishing the respiratory movements of the lower lobe, and in particular its inspiratory aspiration force, as is a

resection of the lower ribs which includes the eleventh rib. In any case, it is clear that the proposal, to begin with a phrenicotomy and follow with a resection of the upper seven or eight ribs, cannot as yet be finally judged for lack of a sufficient number of cases done by this method upon which to form a decision.

Lilienthal and Thearle are the only ones who have adopted this procedure in a reasonable number of cases. Lilienthal believes in it, having had no ill results, but Thearle gave it up, as his results were apparently unfavorable. My own experience has been limited to a few cases, and upon the whole has left me in great doubt as to the validity of Alexander's arguments, however ingenious and theoretically sound they may appear. However, I am able to say that in my series of 78 simple, complete posterior thoracoplasties, done from below upward, there have occurred only two cases of pneumonia or bronchopneumonia, with fatal result. One of these followed a one-stage operation, with death on the eighth day. The second followed the second stage of a two-stage operation, in the seventh week. This represents two deaths in 78 cases, and it should be remarked that cases of partial thoracoplasty, with previous artificial pneumothorax, are not included. The mortality percentage, therefore, is 2.5, and, as the number of operations in these 78 cases was approximately double that number, the operative mortality percentage comes down to 1.3. Including one death in the fourth month, it is 3.3 and 1.7 per cent. It seems to me difficult to expect that any change of procedure, such as that suggested by Alexander, could improve these figures.

But there is another argument which I would beg to put forward. Alexander, as in fact everbody who has worked in this field, goes upon the assumption that cough and expectoration must be encouraged, for fear that the aspiration and stagnation of infected sputum into the lower lobe will inevitably bring about a tuberculous bronchopneumonia. By my own way of thinking, cough, at least during operation and the first twenty-four hours, is more likely to be a danger than a safety. Lipiodol injections have demonstrated that, under the influence of cough or of aspiration, the lipiodol is driven, or drawn, into the alveolar spaces of any part of either lung. This spreading effect of cough is much greater than that of aspiration. Ameuille observed, under the screen, the effect of cough upon an injection of lipiodol. The first cough forced the lipiodol into the upper lobe of the same side, the second drove it into the lower lobe of the other side, while a third cough expelled most of it through

the mouth. I have frequently made the observation that lipiodol, driven by cough into healthy portions of the pulmonary alveoli, remained there for weeks, and in one case for over a year. Now it is clear that thick, tenacious, mucopurulent sputum can hardly be forced deeper than the larger bronchioles, whence it gradually finds its way back into the trachea and is coughed up.[2] Such sputum is most unlikely to spread the disease by contact. On the other hand, fluid tuberculous pus, of a consistency comparable with that of lipiodol, might easily be forced by cough into the healthy alveoli of the lung if it arrived in the trachea in any quantity. Under the ordinary circumstances of taking the cure it is unlikely that more than a small amount of such fluid pus is discharged from cavities at any one time, and this can be coughed up by the patient without particular danger.

But conditions are entirely different during operation. Here a cavity, containing a considerable amount of such fluid pus, may easily, under the necessary operative manipulation, discharge its contents under pressure, and in considerable amount, suddenly into the trachea. If now the patient is being operated on under local anaesthesia, and in the usual head-high position, he may be unable to expectorate the whole amount of pus safely. He may easily, while getting rid of part of it, force some of it into the alveolar spaces of the healthy lung. Once arrived in the alveoli it must be expected, because of the absence of the cough reflex in bronchi below those of the second order, that it will remain there, like lipiodol, for a considerable time, at any rate for days or weeks, and in any case for a quite sufficient time to cause, by contact, an acute tuberculosis. Experiments have shown that tubercle bacilli, in broth suspension, introduced into the nares of a rabbit and arriving by the aspiration of quiet breathing and by the effect of gravity in the lung tissue of the side upon which the animal is laid, do cause an acute tuberculous pneumonia. I suspect that in many of the cases of so called flare-up, following operation, the infection has occurred in the way just described.

It should be remembered also that the expelling power of cough is impaired by rib resection over the upper lobe, in no small degree, although perhaps less than by a resection of the lower ribs, and that this impairment is not prevented by local anaesthesia. There remains also Sauerbruch's original argument that an upper-rib resection, over the usual

[2] Experimental evidence of the correctness of this assumption has since been brought forward by Brown and Archibald in a paper awaiting publication in THE AMERICAN REVIEW OF TUBERCULOSIS.

site of cavities, is apt to express the contents of those cavities which may be aspirated into the lower lobe. The very position of the patient on the operating table, with the diseased side uppermost, favors the emptying of the cavities by gravity. It should likewise be remembered that most operators place the patient on the operating table in an inclined position, with the chest somewhat above the level of the hips, so that any pus coming from cavities is apt to flow down hill, by gravity, and into the lower lobe. I have always, myself, for this reason placed the patient flat on the table, with a pillow under the chest, and the head low, so that pus may rather run out of the mouth than downward to the lung, and the danger of cough in an upright position is therefore the less.

However all this may be, the point of my argument lies in the assump-

TABLE 1

Pneumonia deaths ascribable to thoracoplastic operation

	CASES	OPERATIONS	NUMBER OF DEATHS	CASE PERCENTAGE	OPERATION PERCENTAGE
Total posterior	78	156	2		
Partial posterior	12	13	1		
	90	169	3	3.3	1.7

Remarks as to deaths:

1 and 2 Acute tuberculous bronchopneumonia of good side, previously clear, probably by aspiration; death on 8th day p.o., and in 7th week, p.o.

3 Acute tuberculous bronchopneumonia by aggravation of previously active disease in good lung, in 4th month, p.o.

tion that cough, during the period of probable emptying of fluid pus from cavities, that is, during operation particularly, and also during the first 48 hours when the patient finds it so difficult to lie on the operated side, constitutes at least as much of a danger as a measure of safety.

While these considerations have been borne in upon me only during the last year, since becoming acquainted with lipiodol pictures, I have, nevertheless, almost from the start operated under the principles suggested by these ideas. Whether they are correct or not, I can at least point to the fact that the unfortunate complication of postoperative tuberculous spread has been, in my series, less frequent than seems to have been the case with most surgeons (see table 1).

While, therefore, the argument of Lilienthal, who has for a considerable time been resecting the upper ribs first, and of Alexander, may be theo-

retically correct, I would point out that it is very possibly based upon an incorrect premise, the premise that efficient cough during and soon after operation is the chief factor of safety; and I suggest that we have at least equal reason to believe that efficient cough is a danger.

Upon this basis my practice has been to abolish cough during and for twenty-four to forty-eight hours after operation. I do this by the employment of two doses of morphine, occasionally three, before operation by using general anaesthesia with nitrous-oxide gas and oxygen, and by a very liberal use of morphine for the first twenty-four hours after operation. By this time the patient is able to sit up, cavities are not being actively emptied, the discharge from cavities has at least gone back to normal level or less, coughing power is recovering, and the sputum, by stagnation, has become mucoid and tenacious; in other words, the patient is not much more exposed to the dangers of spreading his own disease than he was before operation.

A third serious cause of death from operation is wound infection. Sauerbruch admits the frequency of some wound infection, and ascribes it to the lowered resistance of many of the patients. Brunner, in his 117 case-reports, mentions the word *Eiterung* forty-six times. Often it was slight, sometimes it delayed healing for a considerable time, and in 6 cases it was the chief cause of death. In my own series of 90 cases I have had two deaths from wound infection, and six other unimportant infections in the wound, of which three were tuberculous. It cannot be denied that Brunner's 46 infections in 117 cases are excessive. On the other hand, nobody can reasonably assert that this is due to an insufficiently aseptic technique. For my own part I am inclined to think that the excessive use of novocaine is responsible in large part, especially when combined with adrenalin. I notice, for instance, that Brunner mentions several times the occurrence of fascial necrosis. Novocaine, like cocaine, may have a necrosing effect, and necrosis predisposes to infection. Adrenalin promotes secondary oozing of blood and the development of subcutaneous collections of serum, which again are favorable to infection. Consequently I have never used more than a minimal amount of novocaine, never exceeding 50 or 60 cc., and for the past year approximately 15 to 20 cc. It is used only to raise a wheal in the skin, and not in the subcutaneous tissue or aponeurosis. For each intercostal nerve I use not more than 1 to 2 cc. and even this I frequently dispense with, finding the gas anaesthesia sufficient. Drainage is always employed for 24 to 36 hours. In this way, as I believe, both novocaine deaths and wound

infections are best avoided. One may be allowed to suggest also that during the deep injection of the nerves, if made through the skin, the needle, if used without caution, may penetrate infected lung and thus introduce microörganisms into the wound. The nerves should not be injected before the ribs are exposed.

There remains to discuss what is, after all, probably the most frequent cause of early death after operation. I refer to that abrupt change in the physiology of respiration caused by the removal of the costal support.

TABLE 2

Deaths ascribable to thoracoplastic operation (exclusive of pyopneumothorax cases)

TYPE OF OPERATION	NUMBER OF CASES	NUMBER OF OPERATIONS	TIME OF DEATH	NUMBER OF DEATHS	CASE PERCENTAGE	OPERATION PERCENTAGE	CAUSES OF DEATH
Total posterior	78	156	1st week	0			1. Acute tuberculous pneumonia on good side, 8th day
			2nd week	2			2. Infected wound, secondary haemorrhage, 9th day
			7th week	1			3. Acute tuberculous pneumonia
Partial posterior with partial artificial pneumothorax	7	8	No deaths ascribable to operation				
Partial posterior as uncompleted operation	5	5	2nd week	1			1. Cardiac failure
			3rd week	1			2. Streptococcus infection of wound
			4th month	1			3. Bronchopneumonia
Total.....	90	169		6	6.6	3.5	

The very serious effects of paradoxical respiration are so well known that I do not need to labor the argument. That the danger from a one-stage operation in this respect is much greater than from one of two stages, and that the advantage of a one-stage over a two-stage operation in the way of compression of the lung, and ultimate cure, is insufficient to offset the added risk, represent principles that are becoming generally accepted. I have allowed myself to do the operation in one stage on only two occasions, and to this I ascribe chiefly the fortunate circumstance that the

operative mortality has been reasonably low. The accompanying table 2 shows what that mortality has been and the causes of death. In any case I conceive that the argument for a two-stage or, if necessary, a three-stage or four-stage operation, as against the one-stage operation, is unanswerable, if one has chief regard for the immediate safety of the patient.

The subject of a proper selection of cases is so large that in this place one can only make a few remarks. Those, who confess to a high operative mortality within the first three or four months, urge in extenuation that they accept a considerable proportion of unfavorable cases in order to give such patients their chance. With that attitude I can have no real quarrel, yet I would point out that *there is a risk of taking away, by operation, whatever chance of life a patient has.* It will often be better at any rate to delay operation and to put the patient upon absolute bed-rest on a frame, as one treats Pott's disease, and to wait for a possible improvement. In the presence of recent activity in the good lung, of the exudative type, I am absolutely opposed to operation. The risk of creating a negative phase, and of hastening the patient's death is too great. I count in my own series many cases in which the destruction of the lung was too far advanced to hope for a good result, and I count a few in which I have operated in the presence of limited active lesions in the good side. The former have not died, although their condition was not sufficiently improved, but a fair proportion of the latter have died from rapid progression of the disease. The selection of cases has, above all, to depend upon the evidence of good resistance. When that is not present it can only result in discredit to an otherwise most beneficent surgical procedure, if one takes an unwarranted chance, and proceeds with a total thoracoplasty.

On the other hand, absolute bed-rest for some months will in many cases result in a clearing up of the active exudative lesions recognized upon physical examination and seen in X-ray films in the good lung, with the result that the patient's chance of recovery is not really taken away by the postponement, but is rather improved by it. And if, during this delay, the active process does not clear up, one may be sure that operation would have done nothing but hasten the development of the disease. In a certain proportion of these cases, in which activity in the good side is at the apex and not in the lower lobe, or in which it is doubtful in any case, Sauerbruch's test phrenicotomy, followed by a sufficient period of observation, is valuable.

I have not considered such rare causes of death as pulmonary embolism, nephritis, intercurrent infections, and fulminating haemoptysis. Each patient should be examined before operation with all the resources of our science, in order to estimate correctly the functional capacity of the kidneys, and particularly of the heart, and any serious lesion in these respects should be a formal contraindication. Against the other post-operative accidents just mentioned, we have no safeguard. I have, fortunately, not had to deplore a death from any of these causes.

CONCLUSIONS

1. Deaths following extrapleural thoracoplasty, as reported, are unnecessarily high.
2. A one-stage operation is now hardly justifiable; its mortality even in favorable cases is excessive.
3. Removal of too many ribs or too long portions of ribs, even in two-stage operations, is responsible for a number of avoidable deaths.
4. Local anaesthesia, *in large amounts*, is responsible for avoidable deaths
   a. By anaesthetic poisoning.
   b. By favoring wound infection and necrosis.
5. Wound infection is best avoided by
   a. A general anaesthetic and very little local anaesthetic.
   b. Greater care in approximation of wound edges.
   c. Not doing too much at one time.
6. Cough during and soon after operation, as regards spread of the disease into the sound lung, is probably a greater source of danger than of safety.

THE TREATMENT OF LARYNGEAL TUBERCULOSIS IN SANATORIA[1]

CHARLES D. PARFITT[2]

The material upon which this paper has been based is a group of cases of laryngeal tuberculosis, observed and treated in two small private sanatoria during a period of seventeen years, between March, 1909, and June, 1926. No restriction was made regarding the admission of laryngeal cases, although exclusion of all patients for whom there was no likelihood of material improvement was the rule.

Of 872 tuberculous patients, 134 (15.4 per cent) had laryngeal tuberculosis and 85 (9.7 per cent) nontuberculous laryngitis. *B. tuberculosis* had been found in all but one of the patients with laryngeal tuberculosis. The general condition was classified after the National Tuberculosis Association's standards as: moderately advanced, 20 per cent, and far advanced, 80 per cent.

The incidence of laryngeal tuberculosis in sanatoria has varied greatly in the published reports. This is no doubt due to the differences in the degree of illness and social conditions of patients at different institutions, to the exclusion of cases of laryngeal tuberculosis in some, to the thoroughness of routine examination, and to the criteria of diagnosis. Publications relating to laryngeal tuberculosis in sanatoria show an incidence varying between 8 and 63 per cent. In a recent study of his ten years' experience at the King Edward VII Sanatorium, Sir St. Clair Thomson found that 17.77 per cent of the patients there had this complication.

Through a questionnaire sent to twenty sanatoria in Canada in 1922, I obtained information regarding 8,393 cases, of which 5.4 per cent had laryngeal tuberculosis. In thirteen of these sanatoria discrimination against the admission of patients with this complication was probably exercised; in these, such cases averaged only 4.5 per cent, while in six institutions in which there was no selection the average was 16.6 per cent.

[1] Presented before the Clinical Section at the twenty-second annual meeting of the National Tuberculosis Association, Washington, D. C., October 6, 1926.

[2] Calydor Sanatorium, Gravenhurst, Ontario.

It is generally conceded that at least one-third of all patients suffering from active phthisis have laryngeal tuberculosis.

Sir St. Clair Thomson makes a striking comparison of the mortality in sanatorium patients between those with and without this complication. The deaths were twice as great, proportionately, in the former group as in the latter, in from one to ten years after discharge. He considers that for prognosis a laryngeal examination may outweigh in importance all other clinical examinations, and, while not necessarily the fatal disease of a generation ago, that laryngeal tuberculosis is, next to meningitis, the most serious complication of pulmonary tuberculosis.

Following the great sanatorium development and the favorable influence of its regimen upon laryngeal cases, it became recognized that laryngeal tuberculosis cannot be treated solely as a local disease and that effective local treatment must be simply an auxiliary to sound general treatment based upon the full appreciation of the pulmonary infection. Vexed opinion regarding the proper mode of treatment of this complication has obtained during the earlier years of this century, the supporters of topical applications and drastic surgical procedures having been strenuously opposed by those who believed only in expectant measures. Both groups, however, now find a compromise in accepting the dramatic possibilities of the galvanocautery. Too great a reliance upon general measures has been too often the rule in sanatoria, to the neglect of rational local treatment. Exceptions to the rule are to be found in those sanatoria which have had a visiting laryngologist within easy access, and in those few in which some interested staff member has been detailed to supervise and develop technique for the treatment of these cases. From the literature one is forced to conclude that, outside the larger health resorts and the occasional sanatoria, the treatment of laryngeal tuberculosis has not been energetic. Yet the literature shows that much may be done for such cases.

In the sanatorium the patient with laryngeal tuberculosis has living conditions and a regimen under which local measures give much more promise of benefit than when they are carried out without these advantages. Atmospheric conditions are improved, and the irritation of tobacco and alcohol is controlled. Prolonged and often intensive bed-rest can be carried out, in the great majority of cases combined with rest of voice, by strict silence or lip-whispering. In two of my cases almost complete silence was persevered in for more than a year. Individual rooms are a great help to this regimen, but with daily encouragement to

persevere some companionship may be maintained. The conditions above the larynx which further laryngeal irritation, emphasized by all writers, can be investigated, referred if necessary to a rhinologist, and treated as a matter of routine. Such treatment may lessen irritation and cough surprisingly. Cough may, even more than talking, aggravate the lesion. Its cause should be carefully sought. Liquefying expectorants and sedatives are usually necessary for a time. Cleansing and sedative sprays, sedative intratracheal injections and insufflations can be undertaken at frequent intervals, as a routine, and given effectively. Such local measures are considered largely unnecessary by Sir St. Clair Thomson, and he deprecates their use. To the occasional patient with painful deglutition, help can be given manually, and by adjustment of posture, and suitable feeding arranged. Instruction and supervision can be given in the use of Dr. Alexius M. Forster's metallic mirrors for reflecting sunlight. This last method of treatment has greatly reduced apprehension in regard to definite or suspected laryngeal tuberculosis in our western provinces in Canada, where it can be promptly and efficiently applied. In Northern Ontario I have used it rather inconsistently, partly because of the difficulty in always taking advantage of uncertain sunshine for infirmary patients.

More active measures will frequently be indicated. Procrastination in their application will sometimes be desirable, yet prompt active interference may gain greater security for the patient, and also save both the physician and the staff much time.

For twenty-five years I have been so placed that regular visits by specialists have been quite impracticable and I have felt obliged to attempt the local treatment of these cases myself. My approach has been that of the practitioner among the tuberculous, whose responsibility is to do what he can to help his patient unaided by the specialist. My bent toward active interference was mainly due to the teaching of Hajek of Vienna in the late eighteen-nineties, and, except in very mild cases, I have never felt it right to rely upon sanatorium treatment alone when it seemed possible to accomplish something by local treatment.

Prior to 1909 I consistently used repeated applications of formalin and other pigments, to infiltrations and ulcers, the surface of the latter being occasionally curetted. The early records of seven years are lost to me. Results sufficiently good to maintain enthusiasm for the methods were obtained, and a number of arrests and cures were effected, progress of the lesion was restrained in many, secondary infection reduced and the

throat made much more comfortable. Voice rest was not enforced during this period. Never were the marked proliferations seen, such as I have seen elsewhere in sanatoria where no active local treatment was undertaken.

The daily application of pigments is very exacting in the matter of time. This is well illustrated in Bulloch's large series, which, however, shows what remarkable results can be obtained by the persistent use of formalin.

The frequent application of formalin and lactic acid to ulcers then became displaced by the occasional use of Lake's pigment (lactic acid 50, formalin 7, carbolic acid 10, water 33 parts) as a time-saver and as being more efficient, and since 1912 this last has again been displaced largely by the galvanocautery. Practice in the application of pigments to suitable cases will give excellent training for endolaryngeal operations. The occasional use of Heryng's curettes will make the applications of pigments to ulcers more effective. Double curettes or punch-forceps are, however, better for the removal of granulomata or tuberculomata as a useful preliminary to galvanocauterization. With the epiglottis punch-forceps of Lake or Barwell, used with or without fixation forceps, one can remove the epiglottis with one punch and give the greatest relief when odynophagia is due to a diseased epiglottis. Eschat's tongue retractor is a help for this relatively simple operation. Pain may remain after the removal of an epiglottis because of a diseased arytenoid. This, possibly, may also be relieved by the removal of a portion of it with Lake's forceps or, preferably, by ignipuncture. The latter is urged by Wood and also Fetterolf as superior to and safer (because it avoids possible dissemination) than epiglottidectomy. Lockard, Lake, and Barwell strongly advocate epiglottidectomy, not only as a palliative measure, but in a considerable proportion of cases as curative, or as helping toward more effective treatment elsewhere in the larynx. The only contraindication is evidence of disease in the folds connecting the epiglottis with the pharynx and tongue. In five cases in which I have removed the epiglottis there was no subsequent difficulty from food entering the larynx, relief was prompt when there was no associated arytenoid disease, and even then some further relief was given either by partial arytenoidectomy or puncture by the cautery.

The galvanocautery has, however, largely displaced all operative measures, and, excepting epiglottidectomy, those undertaken are simply preliminary to its use. Combined with voice rest, the cautery has

made it possible to dispense almost entirely with other time-consuming measures. The adoption of this highly efficient and relatively easy method of treatment has been slow, although it is now becoming widely used, and it is to be hoped that it will become available for all sanatoria. It was, I believe, first used for laryngeal tuberculosis by Voltolini in 1861 and again by Heryng about 1887. Dundas Grant advocated it at the beginning of this century, but it was little used until after Mermod's publication in 1903 and Gruenwald's in 1907. As early as 1905 Harland reported its use at the Henry Phipps Institute.

The object of this method of treatment is not merely the destruction of a certain amount of tuberculous tissue, but the production of a reaction, resulting in improved blood supply and the formation of scar-tissue. The disappearance of tubercle in the cauterized and surrounding tissues has been shown experimentally by Wood. Thomson restricts the use of the cautery to indolent types of lesions, which do not respond within a few months to sanatorium measures, including strict voice rest. He considers it contraindicated in acute types with oedema or pseudo-oedema, and when there is pain and dysphagia indicating perichondritis, and if there is unstable temperature, quick pulse, failing weight or feeble resistance. Wood believes that all types of localized lesions within reach will be more successfully combatted by the cautery than by any other form of treatment, that 90 per cent of incipient cases can be cured, and that the benefits obtainable will be limited only by the ability to reach all the diseased structures, provided that the patient has enough vitality to produce the necessary reaction for healing the burned area. With such reactive power there is no contraindication to cauterization as regards the pulmonary lesion and general condition. I have preferred early cauterization to delay in mild laryngeal lesions with favorable prognosis in regard to the lung disease, in order to save time when the patient cannot long remain under treatment; in ulcerative lesions when invasion of the arytenoids was threatened; and in progressive cases even with fever when local reaction seemed probable. Cauterization has, in grave cases, given some relief to pain when the arytenoids or epiglottis have been involved. When there are no severe symptoms in acute and far-advanced cases operative treatment is unnecessary, and probably prejudicial because of the effort necessary on the patient's part.

When reasonable dexterity in making topical applications or in touching points in the larynx has been acquired, the galvanocautery will not be found difficult to use. The point can be placed while cold, but it

must be removed while hot. During removal the operator must be careful not to scorch the opposite laryngeal surface by the heel of the cautery. The first cauterization should be cautiously undertaken and should be limited when the general condition is much impaired. At all times restraint should be exercised in regard to the number of punctures and amount of surface attacked. The depth of puncture must be controlled in order to avoid burning cartilage. It is best to do rather less than one may feel inclined to do. Only experience can teach the extent and depth of cauterization for different types of lesions and patients. The same area should not be again attacked until healing has taken place and opportunity for contraction given. This will require about a month. Other areas may meanwhile be treated. The reaction is relatively slight. Only once have I seen distress from dyspnoea, when cauterization was combined with a cutting operation in a small larynx. The patient rarely suffers pain at the time and is not fearful of a repetition of the treatment. Soreness afterward subsides quickly and is seldom severe. The technique of anaesthetization and cauterization followed has been developed mainly from the information given by Thomson and Wood. Occasional fiascos have resulted from the too cautious use of cocaine, and cauterizations have been less severe than these writers are wont to make them. Fetterolf mentions having made 350 punctures over a period of months in one case. In my 27 cases there have been only 65 sittings, with an average of about 4 punctures at each sitting. A hypodermatic injection of morphine with atropine has helped the anaesthetization, has lessened the amount of cocaine necessary, has possibly helped to safeguard its use, and has lessened the annoyance of excessive secretion during the procedure.

For palliative treatment Leduc's autoinsufflator for anaesthetic and antiseptic powders, Yankauer's dropper for solutions, and Seymour Jones's apparatus for intratracheal injections of solutions in oil are most useful. The last-mentioned is used by inserting a catheter through a nostril, the point of which, behind the uvula, immediately overhangs the larynx. Mendel's method of injecting the solution behind the anterior pillar of the fauces is also serviceable for intratracheal injection. These several methods can be used by the patient himself. Nerve blocking has given relief, occasionally marked and lasting as long as six weeks, in 60 per cent of the attempts. Epiglottidectomy may be desirable, even when the blocking has been successful, to give full relief.

Prior to 1916 tuberculin in the usual manner was employed in 18 cases.

Its effect upon the local lesion cannot be fairly judged. Artificial pneumothorax had been induced in seventeen of the patients and thoracoplasty in one, on general indications. Nine patients already under treatment by artificial pneumothorax, much to my surprise, developed a laryngeal lesion, and in 5 of these the lesion failed to improve. The result in the 27 cases of lung compression was 14 (52.1 per cent) classed as apparently arrested or better. A curative treatment by cautery or curette was made in three.

I shall omit a detailed analysis of the cases, but should like to make a few comments upon the analysis. The lesions of laryngeal tuberculosis are so varied in site, number, extent, intensity, character and type that it is difficult to deal with them concisely. The terms "mild," "moderate" and "severe" have been used to denote the degree of severity, combined with terms denoting the major pathological characteristic of the lesion.

The grading of the 134 cases in degree of severity was mild in 77 (57 per cent), moderate in 35 (26 per cent) and severe in 22 (17 per cent).

In order to compare the relative effectiveness of different kinds of treatment, the cases have been divided into three groups, which are similarly classified as to lesion. The nonoperative group contains 102 cases (76 per cent), the galvanocautery group 27 (20 per cent), and the operative group 5 (4 per cent). Of the nonoperative group, 67 per cent were of mild degree, while but 26 per cent of the galvanocautery group and 40 per cent of the operative group were in this class.

The object of local treatment in the nonoperative group was auxiliary to sanatorium regimen, only, in 59 cases, curative in 14, and palliative in 3. Twenty-six patients in this group had no treatment. In the galvanocautery group the object of treatment was curative in 19 and palliative in 8 cases; and, in the operative group, only, curative in 2 and palliative in 3 cases.

The terms of the National Tuberculosis Association for classifying results of treatment of pulmonary cases have been used as literally as possible in grading the results of treatment of the laryngeal cases.

Of the 134 cases, 45 (33.6 per cent) have been classified as apparently arrested or higher, 13 (9.7 per cent) as apparently cured, 12 (8.9 per cent) as arrested, 20 (15 per cent) as apparently arrested, 7 (5.2 per cent) as quiescent, 21 (15.7 per cent) as improved, and 61 (45.5 per cent) as unimproved.

Of the 77 cases of mild degree, 28 (37.4 per cent) have been classified

as apparently arrested or better; of the 35 cases of moderate degree, 12 (34.2 per cent); and of the 22 cases of severe degree, 5 (22.7 per cent).

Of the 102 cases of the nonoperative group, 27 (26.5 per cent) have been similarly classed as apparently arrested or better; of the 27 cases of the galvanocautery group, 16 (59.2 per cent); and of the 5 cases of the operative group, 2 (40 per cent).

Twenty-seven patients (20 per cent of the series) have been treated by cauterization during the last fourteen years. The object of this treatment was curative in 19 and palliative in 8. The lesions were two hypertrophies, one infiltration of moderate degree, 5 mild, 8 moderate and 11 severe ulcerations; that is, 74 per cent were moderate or severe lesions. The result obtained in these lesions was an apparent arrest in 5, arrest in 5, and apparent cure in 6; that is, 16 (59.2 per cent) were classed as apparently arrested or better, 3 (11.1 per cent) were improved, and 8 (29.7 per cent) were unimproved. Twelve of the 16 patients, in whom the lesion was arrested, obtained a good voice for ordinary speech with very little alteration in quality. No harm resulted to any patient because of cauterization.

The good results of treatment possible at sanatoria because of their location, regimen and opportunities for local treatment, make them the logical places in which all but absolutely hopeless laryngeal cases should be treated. Moreover, frequent visits to the office of a laryngologist by patients with active pulmonary disease will be prejudicial to their recovery. In all sanatoria, however, if laryngeal patients are to get their due, the opportunity for treatment, especially by the galvanocautery, should be given. Security against the advance of a formidable lesion may thus be more quickly obtained, and more comfort be given to the patient than by any other method. Local heliotherapy is a desirable adjunct to treatment by the cautery, but it is nonessential to its success. However, not all cases are suitable for cauterization, and those are fortunate if the opportunity for local treatment by continuous sunshine can be given them.

In isolated sanatoria and in those not blessed by having an energetic laryngologist on the visiting staff, a staff-physician should be detailed to learn the technique of safe instrumentation and to treat the group of laryngeal cases. With interest and perseverance, facility can soon be learned through practice, first on a dummy and later on patients, with a protected applicator. After much practice of this kind the cautious use of the galvanocautery may be safely undertaken. Specialists are per-

haps quite properly critical of amateurs entering their field and deprecate endolaryngeal work by them, yet Robert Levy, for example, does not disapprove the cautious use of the galvanocautery by physicians not entirely unskilled in laryngological practice. It is certain that unless amateur laryngologists qualify themselves to do such work large numbers of cases of laryngeal tuberculosis, in the aggregate, will go untreated.

Treatment by cauterization has proved to be desirable in approximately 20 per cent of the writer's cases and curative in 60 per cent of these. It has largely displaced less effective time-consuming methods, and more difficult and distressing cutting operations, with the exception of epiglottidectomy.

Most cases of laryngeal tuberculosis seen in a far-advanced stage have progressed from an early stage and a majority of these would have yielded to local treatment if it had been used in conjunction with general measures. Like pulmonary tuberculosis three stages of laryngeal tuberculosis may be recognized and we should diagnose and treat these cases when the disease is curable.

Laryngeal tuberculosis has been one of the less dangerous complications of pulmonary tuberculosis, and the one most amenable to treatment. The lesion often becomes arrested or cured before the patient has recovered from the pulmonary disease, while even those with advanced laryngeal disease and bad prognosis may benefit greatly by active interference. The laryngeal complication has rarely proved to be fatal, and then only in fulminant cases or in those with an otherwise hopeless prognosis. To be able to change certain disaster to relative or complete recovery by a little skilful interference is so much an opportunity for relief of suffering and such a satisfaction, that the treatment of laryngeal tuberculosis in sanatoria deserves every consideration.

A conservative estimate is that to-day there are in this country 25,000 patients with laryngeal tuberculosis, for whom the galvanocautery is needed, more than half of whom should obtain an arrested laryngeal lesion by its use.

THESES ON INTESTINAL TUBERCULOSIS[1]

DAVID A. STEWART[2]

Two and a half centuries ago the Father of Modern English Medicine, writing of consumptions, had this to say:

Lastly, to close the scene, a looseness succeeds, occasioned partly by corrupt humours, discharged from the mesenteric arteries into the intestines, and deposited there, and partly by the weakened tone of the viscera; and thus the patient perishes at length the following summer by a distemper occasioned by the foregoing winter. And this is the principal kind of the disease.

If in our day we are a little wiser than Sydenham about intestinal tuberculosis, and have learned to anticipate and perhaps sometimes to prevent the evil day when "lastly to close the scene a looseness succeeds," it is largely because the light of the X-ray has been flashed across this dark continent of clinical hopelessness by such men as Stierlin, Archibald, Pirie, Brown, Sampson, Carman and Lemon.

This paper is an attempt to restate in small compass as theses something of what the staff of the Manitoba Sanatorium has learned of the intestinal complications of tuberculosis in seven years of fairly intensive clinical study, including nearly 1,500 barium meals. In the latter half of the seven years a barium meal has been given as a routine to all tuberculous patients (nearly 800) on admission. These studies may be of greater interest and use because the one sanatorium of a small province such as Manitoba is a catch-all for every type of tuberculosis and for all stages, from the rare early to the commoner moribund case, with only a few days to live.

Some patients were classed as *Apparently Hopeless*. Of these, 71 per cent had definite symptoms or signs of enteritis, 15 per cent had neither, and 14 per cent were doubtful. It is well known that not infrequently widespread intestinal ulceration is found after death, when

[1] Presented before the Clinical Section at the twenty-second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 6, 1926.

[2] Manitoba Sanatorium, Ninette, Manitoba. Throughout the whole period of these studies Dr. Joseph E. Pritchard and the late Mr. Peter McConnell were most closely associated with the author.

in life no corresponding symptoms had been complained of. But when both symptoms and barium meals are observed at the stage of apparent hopelessness, percentages should approximate those found postmortem. Such percentages vary between the 57 per cent of Fenwick and Dodwell, as well as Eisenbardt, to the 92 per cent of Engelsmann. Schwatt and Steinbach found evidence in 65 per cent. Robert Paterson, summing up many series, concluded that ulceration in the intestines had been found in 75 per cent of cadavers after death from pulmonary tuberculosis. This closely approximates the 71 per cent, or nearly three-fourths, found in our "Apparently Hopeless."

The better type of *Far Advanced*, not so extremely ill, showed roughly one-third with definite signs and symptoms, the *Moderately Advanced* one-third suspected, and the *Minimal* or *Incipient* no suspicious signs.

This we do not consider as proof that intestinal involvement begins with the far-advanced stage of tuberculosis. It shows only that our present appreciation of symptoms and signs is not keen enough to detect it before the far-advanced stage of the pulmonary and intestinal disease has been reached. It may, and likely does, begin much earlier.

It is true that the day and hour of the active beginnings of tuberculosis knoweth no man; but, as manifest in symptoms, the more chronic the disease the more likely it is that enteritis will complicate; the less chronic, the less likely. A main disease that runs from early to hopeless in a year has a one-in-four chance of enteritis. The same course in five years gives a three-in-four chance of enteritis. Some escape it by the time limit. Our histories show the *apparent* onset of intestinal disease averaging twenty-seven months later than the *apparent* onset of pulmonary disease. The onset of the two appears to be simultaneous in only one case in ten.

It is not unusual for a man to carry old, apparently healed pulmonary lesions, with something like impunity, or gross and growing lesions without illness, and suddenly come crash when symptoms of intestinal ulceration appear. The champion goes down at last to a blow below the belt.

In our series were many cases of pleurisy, with and without effusion; tuberculous peritonitis, favorable, severe and even fatal; tuberculosis of bone and joint, kidney, testicle and eye, mostly with some pulmonary involvement, and several seriously ill. Of all these none had definite signs or symptoms of enteritis. Intestinal ulceration seems to accompany and follow pulmonary disease. It has been reported in cases in

which pulmonary lesions were not demonstrated. We have found no such cases, and suggest that a closer study might have shown at least healed lesions in lungs or hilum.

I can well believe, however, that patients with no evident stigmata of tuberculosis may turn up in clinics and consulting rooms not infrequently with vague chronic intestinal distresses actually due to tuberculous ulceration. In a general clinic series of 1,300 such cases a few years ago Groover and Christie found as many symptom complexes explainable by tuberculosis as by gastric and duodenal ulcer together.

Gastrointestinal distresses in pulmonary tuberculosis may well be named legion, for they are many. What experience any of us may have had, especially in an earlier day, must have impressed us with the frequency, the early appearance, the persistence, and the grave prognostic import of gastrointestinal symptoms. Old sayings full of ripe experience, many of them I think coined by Lawrason Brown, have it that "the road to recovery lies through the stomach," that "the best friend of the consumptive is a good digestion," that "poor eaters do badly," that "a flux of the bowel tends to a fatal outcome," and that "digestion is the keystone of the prognostic arch." In 3,000 patients, mostly with advanced disease, Phipps Institute observers recorded impaired appetite in 48 per cent, gastric disturbances in 65 per cent, constipation in 31 per cent, and diarrhoea in 12 per cent. Reasons for seeking treatment given by one thousand tuberculous patients in Saskatchewan were definitely gastrointestinal in 12 per cent and partly gastrointestinal in 35 per cent more.

It is true that a large part of this total of disturbances may be due to many causes besides tuberculous ulceration. The unfortunate tuberculous must be allowed to suffer from some ills outside of their main disease. General toxemia impairs appetite; gastric anacidity can account for diarrhoea, and inactivity for constipation. Damming of the duodenum by pressure of the superior mesenteric vessels can cause distress, especially in bed patients. And other offenses must needs come also. But, after all allowances are made, intestinal ulceration is a common and sinister complication of pulmonary tuberculosis, and the fight will be fought out very often, and won or lost, not so much in the lung cells as in the intestinal mucosa.

SYMPTOMS

With the plain, old classical signs and symptoms, anorexia and nausea, tenderness and pain, diarrhoea and emaciation, foul-smelling stools and a sudden collapse, we are, or were, all too familiar. These are not early and diagnostic signs, but late and prognostic omens. They are as late signs of intestinal ulceration as bubbling râles and cavities are of pulmonary ulceration. If we are not aware of serious trouble until these are established, and complained of, we are just where our grandfathers were with consumption a half-century ago, and intestinal ulceration is still a hopeless condition. For here, as elsewhere, a diagnosis is of real use only when it is made early. The symptoms best worth discussing are the border-line symptoms.

The earlier symptoms we consider are usually referable to small-bowel lesions, the later to large-bowel lesions. Ulceration in the small bowel tends to dam back the flow; in the large bowel, to accelerate the flow. Among the earlier symptoms are gradual and slight changes from the patient's normal temperament toward nervousness and irritability, from usual bowel habit toward constipation. Appetite begins to lag. There may be a beginning of dyspepsia, a feeling of discomfort after meals, gas, failure to gain weight under suitable conditions, and a general "not doing well" for which no other special reason can be found.

In a group of our patients in whom symptoms were studied intensively, nervousness, often real irritability, was found in four out of ten. When a patient, usually placid, begins to be irritable, nervous, querulous, we have come to think first and chiefly of intestinal ulceration as a likely cause. It is an old dictum that disease above the diaphragm is characterized by optimism, disease below the diaphragm by pessimism.

Poor appetite was complained of by seven out of ten in this series, and was the first symptom noted in half of these. It was not so much an entire distaste for food that was complained of as an appetite too easily satisfied. Abnormalities of appetite other than anorexia should be looked upon with suspicion. In one of our patients a typical picture of widespread ulceration, with all the usual gross symptoms, including anorexia and indeed nausea, was preceded by months of ravenous appetite.

Constipation was in the history or the symptom complex of nearly half, and a first symptom in nearly one-third. Constipation, it is true, is a common complication among bed patients, but when it has a noticeable onset or marked increase, while living conditions are unchanged.

and is persistent, its significance as a possible early symptom of ulceration should not be overlooked. Archibald has taught that constipation is a special symptom of ulceration in the small bowel, while diarrhoea is a symptom of ulceration in the large bowel. Alternating diarrhoea and constipation may, he thinks, indicate ulceration in both tracts, a common condition. These symptoms, *nervousness*, *slight impairment of appetite*, and *constipation* beyond usual, form, in our experience, the most valuable early diagnostic triad.

Discomfort was complained of by seven in each ten and was the earliest symptom noted in about fifteen per cent. It was described usually as a "vague sense of discomfort or weight or fulness about or below the umbilicus."

Definite pain was found sooner or later, mostly later, in 90 per cent of the series, though it was the first symptom noted in only 10 per cent. It was usually crampy, complained of in the lower abdomen, and often considered due to gas. It came on at regular intervals after meals, and was usually worse later in the day. A point of great importance is that these pains, while present, were often so slight as not only not to cause complaint, but were sometimes even admitted or described only after close questioning.

Flatulence was noted in more than half, *nausea* in nearly half, and *vomiting* in about one-fifth, but none of these symptoms appeared early.

Diarrhoea, next to pain, we found the most common symptom, present in nearly all cases. It was not an early symptom, but definitely a late one. The beginning of diarrhoea, following upon the carlier constipation, was at times welcomed by the patient as an improvement in his condition.

Physical examination showed little, though tenderness in the abdomen, usually slight, was found in half the series. Examination of stomach contents and of feces added little of significance, and had little diagnostic value except that of ruling out other causes of diarrhoea.

DIAGNOSIS

Such, then, are the outstanding symptoms, but if there is one consideration about symptoms that needs emphasis beyond all others, it is this,—that even *the earliest symptoms must be anticipated.* We must take the initiative. We must go to meet them. The digestive functions of even the moderately healthy have so many vagaries; lapses from the straight path of virtue in diet can be so easily blamed for bowel irregu-

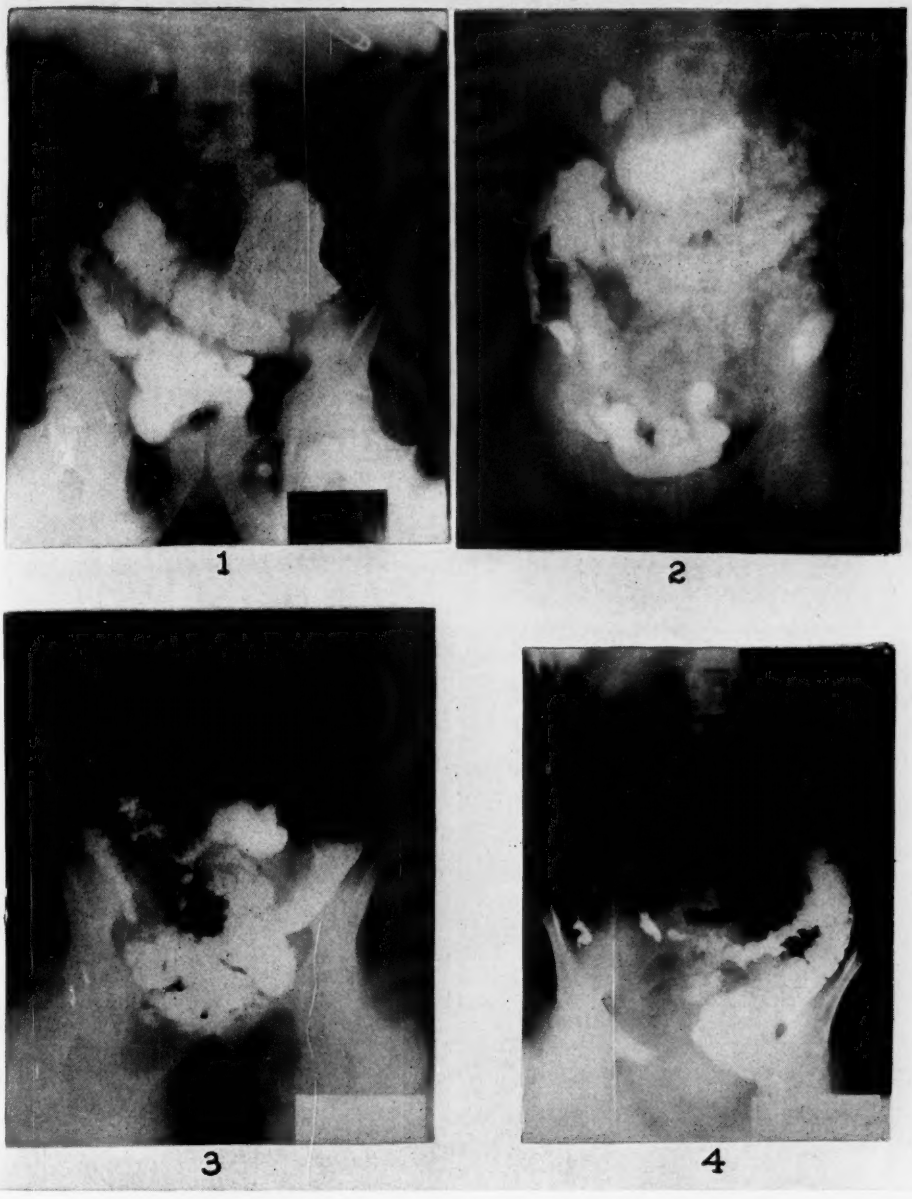

FIG. 1. MEAL AT SIX HOURS. Shows very defective filling of cecum, ascending colon and hepatic flexure as well as segmentation in ileum.

FIG. 2. MEAL AT EIGHT HOURS. Shows gastric retention, segmentation in ileum, very defective filling of colon, especially cecum and ascending portions. This whole very abnormal picture is typical of old and rather chronic tuberculous enteritis.

FIG. 3. MEAL AT TWELVE HOURS. Shows hypermotility and very defective filling of colon. This plate made the diagnosis of tuberculous intestinal ulceration definitely in a girl of eighteen, who had gross pulmonary tuberculosis but who had not up to this time, nor at any time until she died, any other sign or symptom of involvement of intestines. This illustrates, as do the next two figures also, the very great diagnostic value of a barium meal *as a routine measure.*

FIG. 4. MEAL AT TWELVE HOURS. Shows hypermotility and defective filling throughout large bowel. The barium meal made the diagnosis of extensive ulceration absolute in a girl with advanced pulmonary disease, in whom there had been no other symptoms or signs whatever of intestinal involvement, except a day or two of slight diarrhoea.

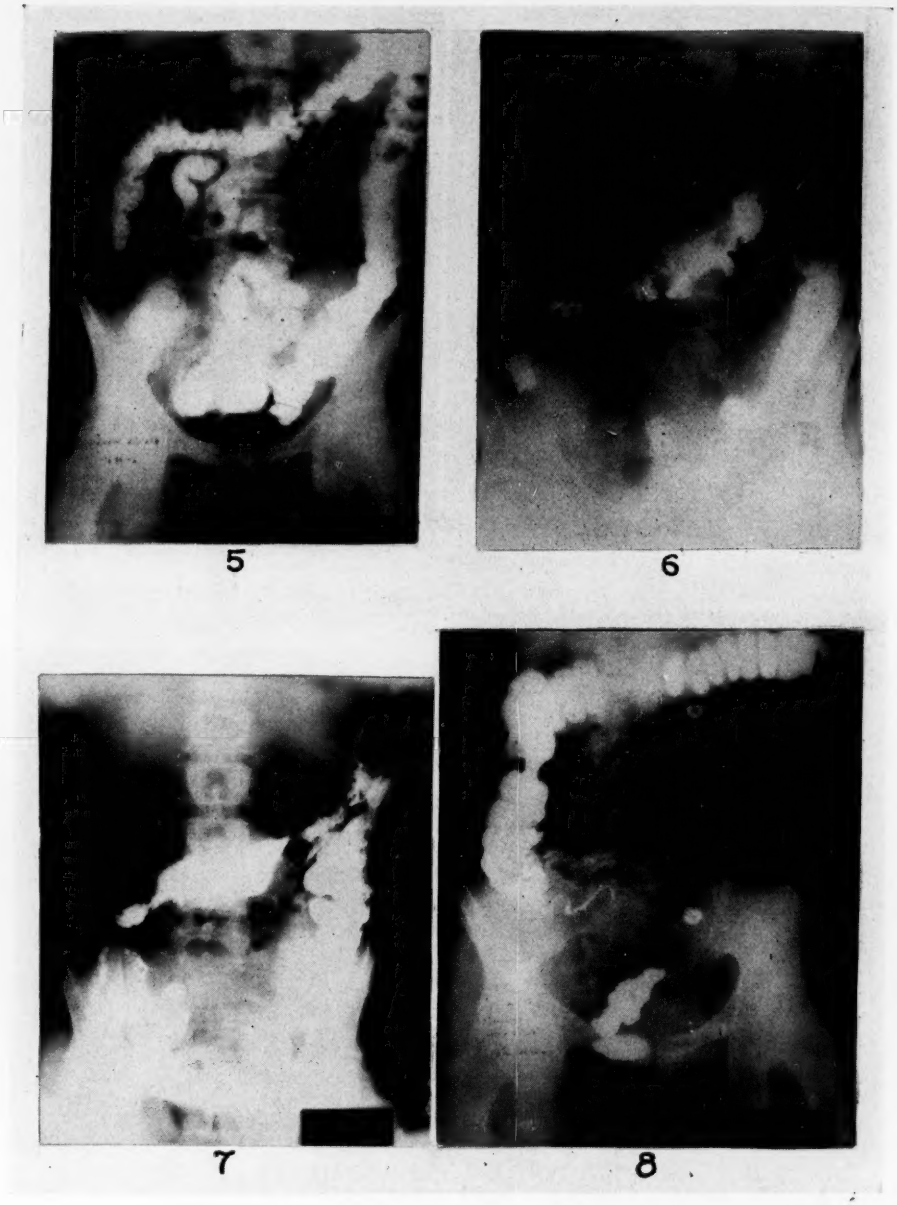

FIG. 5. MEAL AT NINE HOURS. Shows hypermotility, segmentation in ileum, and defective filling in colon. At this time there was advanced disease in the lungs, but no symptoms, signs or history suggesting intestinal involvement. Diagnosis, made by barium meal, was confirmed six months later by the appearance of typical symptoms, which gradually disappeared under treatment, and still later barium meals showed a return toward normal in the bowels.

FIG. 6. MEAL AT SIX HOURS. Shows hypermotility and very defective filling throughout the whole of the large bowel. Symptoms very marked. Condition confirmed at operation (unilateral exclusion). Recovery.

FIG. 7. MEAL AT NINE HOURS. Shows hypermotility and defective filling throughout whole colon. Symptoms marked.

FIG. 8. MEAL AT NINE HOURS IN SAME PATIENT AS OF FIGURE 7 NEARLY TWO YEARS LATER. Shows almost normal filling. Symptoms in the meantime had gradually cleared up.

larities; the changes due to ulceration are at first so slight and insidious, and nervous manifestations so apt to be considered as mere lapses in self-control, that symptoms of intestinal tuberculosis may not be even mentioned to the physician for three, or six months, and not complained of for six months or a whole year after they could have been elicited by careful questioning. This is a diagnosis that is up to the physician, not to the patient.

So much for symptoms. What about the barium meal, and shadows in the fluoroscope and plate? When a bowel has patches of ulceration scattered along its inner surface, or conglomerated, especially near the valve; when its walls are infiltrated, constricted and adherent; it is not surprising that filling defects should be found, or that they should be of definite type, that spasm should cause delay, or a meal be hurried over ulcerated areas, or that the schedule of the meal should be greatly changed.

How much can we depend upon the shadows of barium-filled bowels? How wide or deep has the lesion to be, to leave a clear record on the photographic plate? Within what bounds may the bowel filling or movement be considered normal? How are variations from other causes to be distinguished from those due to tuberculosis? Which gives more information, the meal or the enema? On what routine and at what times can observations best be made? Are there any barium indications of ulceration in the upper bowel?

In comparison with the meal, we consider the enema almost useless. What the enema does show, the meal shows more clearly, easily and often.

So far we have given the single meal, but much may be said for two or three follow-up meals. They can be observed at more convenient times, and perhaps also give the bowel a fairer chance to show its maximum fillings. They make, however, a more complicated picture, and one more difficult to read.

If a single meal be given,—and it seems to us sufficient,—the period of occasional observation must extend from at least the fifth hour to the twelfth or fourteenth hour. It cannot possibly be crowded into an eight-hour day, except by giving the meal at an earlier hour, say two to three A. M. To give a meal at nine A. M. and observe only until four P. M., as is done in some hospitals, is merely to waste material. Indeed, it is worse than that; it is to be misled. In the more gross cases observation at five or six hours is useful. The ninth-hour observation

is instructive and necessary, but the twelfth is usually the most useful of all. We make plates when there is most to record, whatever time that may be, and that is usually at the ninth, twelfth and twenty-fourth hours. In subsequent series in the same patient plates are made, as far as possible, at exactly the same hours, so as to facilitate comparison.

From the reports of many pathologists it would seem that the cecum and ascending colon form the chief storm-centre of ulceration, at least so far as the large bowel is concerned. We consider that we learn most from the behavior of the meal in that region. A well-rounded, smooth-walled cecum, still fairly filled after twenty-four hours with the tail of the meal, comes as near as any barium appearance can to establishing a negative diagnosis. A ragged, dwarfed, shrivelled cecum, a cecum that does not fill, or that empties quickly, that seems intolerant of barium, pretty much makes the diagnosis. Variations at the right or ascending side of the large bowel are more significant than at the left or descending side.

Gastric retention suggests irritation further down, which can very well be due to ulceration in the small bowel. Segmentation, especially in the lower ileum, suggests damming due to ulceration. An ulcerated area tends to retard flow above and accelerate it below, and thus cause constipation or diarrhoea or alternation between them, according to position and extent.

A number of barium meals given to normal controls (if medical students can be so described) shows normal variation fairly wide, and so tends to keep readings of pathological changes conservative. What few operations or autopsies we have had show lesions corresponding fairly well with readings.

If it be objected that ulcerative carcinoma and chronic ulcerative colitis give much the same signs as intestinal tuberculosis, it may be replied that we still make chest plates, though bronchiectasis, abscess and actinomycosis may occasionally have to be differentiated from pulmonary tuberculosis.

The barium meal has been referred to as, "a refinement that is by no means always necessary, and involving fatigue that may prove injurious." Under hospital conditions, and with proper management, it need never be injurious. It may not be an absolute necessity when symptoms already make the diagnosis sufficiently, though even here it is a wonderful teacher of pathology. But when there is doubt, it is a necessity, if correct diagnosis may be considered a necessity.

And the meal has its very highest value, indeed a tremendous value, when given as a routine in all tuberculous cases just as chest plates are made as a routine. It seems to us indispensable. In one in five of our positive cases the diagnosis was made first by barium meal, and in most of these abundantly confirmed after an interval of months by the appearance of symptoms. On the very first day on which symptoms are mentioned to the physician, or even observed by the patient, plates very often show evidence of widespread ulceration. As has been already stated, lesions have been found after death when there have been no symptoms before death. There is a good deal of reason for saying that, in some cases, when symptoms begin lesions have already become gross. To wait for symptoms is to wait months beyond a time when a diagnosis can be made by the barium meal. The only proper method is to anticipate symptoms, discover the disease before it is gross enough to show them, and make the diagnosis without them. We find pulmonary disease that is anything like early only by examining those who are not yet aware of illness; and, if we are to find intestinal tuberculosis anywhere near its beginnings, it will be only by routine examination of those who have not yet begun to complain.

TREATMENT

The first principle in treatment, when the least or earliest sign of symptom or suspicion of intestinal ulceration arises, is that double stress must be laid on all the ordinary means of cure. Rest *is* the cure; and treatment of tuberculosis is primarily and essentially a matter of regulating rest and exercise, of saying whether a patient shall have "typhoid rest," scarcely allowed to whisper, or permitted to do a day's work, or where between these two extremes is the measure of energy expenditure that belongs to his condition. When intestinal signs appear bed-rest is the only possible routine. Results will improve as we are able to give rest earlier, longer and more completely. The great value of earlier diagnosis is earlier doubling of emphasis on *Rest.*

Dietetic treatment has been, as a rule, very disappointing. To give as much intestinal rest as possible Webb recommends milk, three to four ounces every waking hour. We have found of very great value the so called "smooth" or cellulose-free diet of Alvarez, which aims to supply the necessary nourishment with the least intestinal irritation and work. It is small in bulk, high in calories, fairly varied, easily prepared,

palatable, and easily assimilated. With cellulose pretty much removed, the starches are acted upon more freely. If bulk is needed agar can be added. It seems to lessen flatulence, discomfort and bowel irregularities.

Drugs of almost every kind have been used,—antiseptics, sedatives, astringents, opiates and even lubricants,—but for the relief of symptoms rather than for the cure of disease.

Surgery came, and has almost gone. Hyperplastic conditions, stricture of the small bowel due to ulceration, and tuberculous disease of the appendix, have long been submitted to operation with varying success, but the resection and exclusion of an ulcer-studded segment of a tuberculous bowel, in order, by putting it at rest, to promote healing, was a comparatively new application of surgery introduced by Archibald. Though some brands have been plucked from the burning, and others may be, these operations have, for better or for worse, been almost abandoned. I believe that surgery still has a place, but just what that place is might be difficult to define. In acute progressive ulceration, with troublesome symptoms, and a lung lesion fairly quiescent, the chance of operation may be taken. No other treatment can overtake the disease; general measures are slow; it may be surgery or nothing. But for the most part those with pulmonary lesions and active intestinal disease are poor surgical material.

We had just begun to wonder whether surgery could help when a new therapeutic agent topped the horizon. The sun arose; and surgery passed, temporarily at least, into eclipse. The oldest means of cure, light, has become the newest. We return to the armamentarium of Herodotus. It is difficult to analyze the various elements in the "cure" of a bed patient on a sanatorium balcony, and appraise the value of each. But the benefits of light, especially sunlight, in the treatment of intestinal tuberculosis are abundantly evident. Pains are lessened, discomforts tend to disappear, diarrhoea clears up, fever tends to subside, appetite improves, and there is gain in weight. Light is absolutely indicated in all definite or even suspected cases of intestinal tuberculosis, and it should not be denied, where it can be given, even as a palliative, and even to the apparently hopeless.

PROGNOSIS

The literature on intestinal tuberculosis is a favorite stamping ground for gloomy Jeremiahs; no wonder, when many such studies are based

upon postmortem findings only. From such a study of the dead, Schwatt and Steinbach conclude that "the prognosis of ulcers in advanced pulmonary tuberculosis is invariably bad. The onset of this complication ushers in the termination of the case within from three to six months." Similar postmortem studies of pneumonia or of typhoid might base just as gloomy forebodings. And the symptoms these authors mention are all gross symptoms. Therefore, the prognosis of intestinal tuberculosis is about what the prognosis of consumption was fifty years ago, and for the same reason,—that the only stage under observation is the very far advanced.

At present, perhaps, not quite one-third of those who have this complication recover, though in our series fully half made marked improvement, at least temporarily. But it must be borne in mind that when enteritis is present, so, almost always, is advanced pulmonary tuberculosis. Indeed this is the senior and usually the dominant partner.

But if both diagnoses, the pulmonary and the intestinal, were only made earlier; if, especially, the diagnosis of intestinal ulceration were made by routine barium meals and plates months before symptoms would be gross enough to be evident; and if at these earlier stages all means of cure were immediately accentuated, the story could certainly be a brighter one. Tuberculous lungs heal; even gross lesions clear up. Tuberculous lesions in the intestines tend also to heal, and can be shown by barium meals to have healed. Even pulmonary *plus* intestinal disease is recovered from. If the whole story were known, tuberculous intestines may heal as often as tuberculous lungs and both come and go without marked changes in symptoms.

It is possible, but not altogether probable, though indeed likely, that intestinal infiltration may follow fairly closely, and fairly frequently also, upon early pulmonary infiltration; that the two conditions may run the course of the disease very often together, the intestinal more hidden and later in causing symptoms than the pulmonary, but sometimes becoming the dominant phase; and that the intestinal disease may be as improvable and curable, and as often improved and cured, as the pulmonary. At any rate, such a way of thinking will lead us in a better direction than the old one in which intestinal disease appeared always late, was always, if present, blamed for the knock-out blow, and always considered fatal. We are still making the diagnosis usually at a late, almost hopeless stage. By methods we now have, especially routine barium meals, we could make it much earlier. More study

given to these problems would better our methods and add new ones. If we can attain real early diagnosis there is no inherent reason why intestinal lesions should not yield to treatment just as pulmonary lesions do, not always, but often. Methods of treatment are undoubtedly improvable also. At any rate, intestinal tuberculosis is no dark continent of utter hopelessness and despair, but will become increasingly clearer with what time and thought and care we may spend upon it. Here is a wide new region for adventurous young men to explore.

TUBERCULOSIS CASE-FINDING IN CHILDREN[1]

HENRY D. CHADWICK[2]

Two years ago, the Massachusetts Department of Public Health began what is termed its "Ten-Year Program." Its primary purpose was to find those children who showed some evidence of tuberculous disease. Its objective was to prevent the onset of pulmonary tuberculosis in later years by the early recognition and treatment of the children while the disease was yet in the lymph-node stage.

Experience at the Westfield State Sanatorium, over a period of fifteen years with the care of tuberculous children, and some work which we did in 1920 in examining underweight children in the schools in Westfield and other Hampden County towns, showed that there probably was some relationship between malnutrition and tuberculosis.

It would, of course, be desirable to examine all children for evidences of tuberculosis, but as that was too comprehensive a plan to be practical it was decided to examine only the following groups:

1: Children 10 per cent or more underweight for height.

2: Contacts, that is, those known to be exposed to human tuberculosis in the homes.

3: Specials, that is, those not in either of the above-named classes, but who were known to be in poor health.

This plan reduced the number to be listed for examination to about 15 per cent of the school population in the elementary grades. The high schools were not included in this survey.

Preliminary Work: After the lists were made out, the local nurses visited the parents and obtained a signed request for the examination of the chest, a tuberculin test and an X-ray. At the same time, the family and personal histories of the child were obtained.

Clinic Personnel: The first year this consisted of seventeen persons. Of these, five were physicians, one of whom acted as chief of clinics, and the other four as examiners; three were nurses, one of whom acted as

[1] Presented before the Sociological Section at the twenty-second annual meeting of the National Tuberculosis Association, Washington, D. C., October 7, 1926.

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advance agent in the field work; four were stenographers, two of whom worked in the field with the clinics and two wrote the reports in the office; four were nutritionists, who interviewed the parents who were present with their children; and one was an X-ray technician, with a portable machine, who took the films in the buildings where the clinic was held.

The reëxaminations during the second year made necessary the addition of one more physician to this staff.

Clinic Procedure: Examinations were made in the school buildings selected by the local school authorities. It was planned to work only during school hours. One hundred and thirty children were scheduled for a day's work. This number had to vary somewhat, according to the number of children to be examined in the school district. The children from the smaller schools were taken to the larger central buildings. The local school and health-department nurses aided in getting the children to the clinic.

Examinations: The children were stripped to the waist and a cape was thrown over their shoulders while waiting. They were then weighed and measured and the temperature was taken. The physician examined the teeth and tonsils, looked for evidence of adenoids, goitre, enlarged cervical lymph nodes and heart murmurs, and then examined the lungs by auscultation and percussion, paying special attention to the interscapular region for evidence of diseased mediastinal lymph nodes. The findings were recorded on the clinic record sheet. From his physical examination the physician noted that, in his opinion, it was a suspicious or a negative case. No more definite diagnosis as to tuberculosis was made by him. The Pirquet tuberculin test was then made, using full strength Old Tuberculin obtained from the Saranac Laboratory. On the third to the fifth day, the children were again seen by one of the physicians and the results of the test were recorded. A list was made of the reactors and, as soon as possible thereafter, an X-ray film of the chest was taken.

Classification: This was done by the chief of the clinics, who interpreted the X-ray films and reviewed all the evidence. The diagnosis was arrived at by the consideration of the history, symptoms, physical examination, tuberculin test and X-ray and the elimination of other conditions simulating tuberculosis. The standards for diagnosis, as recently published by the National Tuberculosis Association in its sixth revision, were used in classifying all the tuberculous conditions that were found.

Reports: A report of each examination made was sent to the parents,

giving in detail any pathological conditions found, with the recommendation that they consult their physician for advice and treatment. A copy was filed with the board of health, the superintendent of schools and the school principal, so that the public-health nurses could follow up the children found to be in need of special attention.

TABLE 1

Summary of result of the first year's examination

	URBAN		RURAL		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Number of children examined	8,519	84.3	1,579	15.7	10,098	100.0
Number of boys examined	3,589	42.1	642	40.6	4,231	41.3
Number of girls examined	4,930	57.8	937	59.3	5,867	58.5
Number of children with positive Pirquet (reactors)	2,235	28.8	424	28.3	2,659	28.5
Number of children with negative Pirquet (nonreactors)	5,510	71.1	1,073	71.6	6,583	71.3
Number of children who refused Pirquet test	774	9.09	82	5.2	856	7.1
Total number of contacts examined	1,264	16.3	293	19.6	1,557	17.9
Number of known contacts in the reactors	595	26.6	123	29.0	718	27.8
1. Number of immediate contacts	533	23.8	116	27.3	649	25.5
2. Number of remote contacts	62	2.8	7	1.7	69	2.2
Number of known contacts in the nonreactors	669	12.1	170	15.0	839	13.7
1. Number of immediate contacts	581	10.5	152	14.1	733	12.3
2. Number of remote contacts	88	1.6	18	1.7	106	1.6
Number diagnosed as hilum tuberculosis.	410	5.2	75	5.0	485	5.1
(Percentage of reactors)		18.2		17.6		17.9
Number diagnosed as suspects	1,080	13.9	177	11.8	1,257	12.8
(Percentage of reactors)		48.3		41.7		45.0
Number diagnosed as pulmonary tuberculosis	25	0.32	1	0.07	26	0.19
(Percentage of reactors)		1.1		0.23		0.66
Number with visible cervical lymph nodes	494	6.3	120	8.0	614	7.1
1. In reactors	151	6.3	47	11.0	198	8.6
2. In nonreactors	343	6.2	73	6.7	416	6.4
Number of children with asthma	97	1.25	44	2.9	141	2.0
1. In reactors	36	1.6	16	1.4	52	1.5
2. In nonreactors	61	1.1	28	2.6	89	1.8
Number of children with defective teeth	4,051	47.5	668	42.3	4,719	45.0
Number of children with enlarged and diseased tonsils and adenoids	2,235	26.2	488	30.9	2,723	28.5
Number of children with tonsils and adenoids removed	2,752	32.3	529	33.5	3,281	32.9

TABLE 1—*Continued.*

Summary of result of the first year's examination

	URBAN		RURAL		TOTAL	
	Number	Per cent	Number	Per cent	Number	Per cent
Number of children with poor posture...	4,886	57.3	995	63.0	5,881	60.1
Number of children with heart murmurs.	139	1.6	29	1.18	168	1.7
Possible etiological factors for these heart murmurs:						
1. Tonsilitis.....		34.5		44.7		39.6
2. Scarlet fever.....		1.58		17.2		16.5
3. Rheumatism and chorea.....		15.1		6.1		10.9

TABLE 2

Summary of result of the second year's examination

	TOTAL	PER CENT
Number of children examined.....	19,073	
Number of contacts examined.....	2,955	
Number given Pirquet test.....	18,601	
Number of children with positive Pirquet (reactors).....	5,314	28.5
Number of children X-rayed.....	5,730	
Number cases diagnosed as pulmonary tuberculosis.....	19	0.1
Number of cases diagnosed as hilum tuberculosis.....	621	3.3
Number diagnosed as suspects.....	1,399	7.0
Number of cases X-rayed and classified as negative.....	3,691	
Number of children with enlarged and diseased tonsils and adenoids.....	3,652	19.0
Number of children with defective teeth.....	8,575	45.0
Number of children with heart murmurs.....	398	2.0

COMMENT ON THE FIRST YEAR'S WORK

Although there are more boys than girls in the schools of Massachusetts, 17 per cent more girls than boys were listed for examination. This must mean that more girls are underweight than boys, and, taken in connection with the fact that the death-rate for girls is twice that of boys in the age-group 10 to 19 years, may have some significance as indicating that malnutrition furnishes good soil for the development of tuberculosis.

The percentage (28.5) of reactors is lower than anticipated, and would indicate that there is much less infection now than statistics have shown to be the case in former years. This is further emphasized by the knowledge that 17.9 per cent of the children tested were reported to be contacts.

At the age of five there were 18 per cent, at age ten 32 per cent, and at age fifteen 39 per cent reactors. The percentage of reactors (28.8 in urban and 28.3 in rural children) is practically the same.

Cervical Lymph Nodes: Only lymph nodes large enough to be visible were tabulated. Of 614 children with visible lymph nodes only 32 per cent reacted to the tuberculin test. This shows that enlarged cervical lymph nodes are more often caused by other infections than tuberculosis. It is noteworthy, however, that 11 per cent of the rural reactors had visibly enlarged lymph nodes and but 6.3 per cent of the urban children. The rural children showed 4 per cent more enlarged or diseased tonsils, and 1 per cent more of them had had their tonsils removed than had the urban children.

COMMENT ON THE SECOND YEAR'S WORK

The results of the second year's work, when nearly 20,000 were examined, have not been tabulated in detail, as yet, but the figures, as far as shown, vary little from the percentages shown during the first year. It is remarkable that the percentage of reactors (28.5) is the same for the 10,000 children examined the first year as for the 20,000 examined the second year.

TABLE 3

Relation of contact and underweight to the Pirquet reaction

WEIGHT	TOTAL EXAMINED	TOTAL REACTORS	PERCENTAGE OF REACTORS IN TOTAL	TOTAL CONTACTS	PERCENTAGE OF CONTACTS IN TOTAL	NUMBER OF REACTORS IN CONTACTS	PERCENTAGE OF REACTORS IN CONTACTS	TOTAL NONCONTACTS	NUMBER OF REACTORS IN NONCONTACTS	PERCENTAGE OF REACTORS IN NONCONTACTS
Over-average	778	239	30.7	335	43.0	150	44.8	443	89	20
Average	5,459	1,366	25.0	826	15.1	376	45.5	4,633	990	21.3
Seven per cent under	2,095	568	27.1	203	9.6	95	46.8	1,892	473	25.0
Ten per cent under	2,065	615	29.7	177	8.5	91	51.4	1,888	524	27.7
Fifteen per cent under	1,052	332	32.0	78	7.4	37	48.1	974	295	30.3
Totals	11,449	3,120	27.2	1,619	14.1	749	46.3	9,830	2,371	24.2

EVIDENCE OF TUBERCULOUS INFECTION

Table 3 presents an analysis of 11,449 children, who were given the Pirquet test, to show the relation of the reaction to underweight and con-

tact. It is to be noted that in the overweight group there were 43 per cent of contacts and that 44.8 per cent of these reacted to the test, as compared with 20 per cent in the noncontacts of the same group. The percentage of reactors in the whole group examined varied very little in the different weight groups. There was also very little difference in the percentage of reactors in the contacts in the different weight groups; but, when the contacts are excluded, there was a gradual increase in the percentage of reactors from 20 per cent for the overweights to 30 per

TABLE 4

	TOTAL EXAMINED	HILUM	PERCENTAGE	SUSPECTS	PERCENTAGE	PULMONARY	PERCENTAGE	NEGATIVE	PERCENTAGE
Percentage of hilum tuberculosis, suspects, and pulmonary tuberculosis, according to sex, in total number examined									
Male	4,794	242	5.04	2,056	42.8	7	0.014	2,489	51
Female	6,655	311	4.6	2,683	43.3	28	0.042	3,633	54.5
Totals	11,449	553	4.8	4,739		35		6,122	
Percentage of hilum tuberculosis, suspects, and pulmonary tuberculosis, according to sex, in contacts									
Male	763	98	12.7	354	46.3	1	0.013	310	40.6
Female	856	135	15.7	363	42.4	5	0.058	353	41.2
Totals	1,619	233	14.4	717		6		663	
Percentage of hilum tuberculosis, suspects, and pulmonary tuberculosis, according to sex, in noncontacts									
Male	4,031	144	3.5	1,702	42.2	6	0.014	2,179	54
Female	5,799	176	3.03	2,320	40	23	0.039	3,280	56.7
Totals	9,830	320	3.2	4,022		29		5,459	

cent for the 15 per cent underweight group. This is enough difference to appear to have some significance. We cannot conceive how an underweight child would have more opportunities to become infected than one of average weight.

We assume that a child's growth may be retarded because of the tuberculous infection to which it has not yet become adjusted. That this handicap, however, does not necessarily continue is evidenced by the fact that there were 45 per cent reactors in a group of 1,169 overweight

and average-weight children, who were exposed to tuberculosis in their homes, and, therefore, presumably subject to more certain and continuous infection.

We must conclude, therefore, that underweight does not predispose to infection, but that a child may be underweight because of what may be called uncompensated infection, or of an unrecognized, incipient tuberculosis in some part of the body. As underweight children, as a group, show more infection than those of average weight, and because malnutrition may be assumed to furnish favorable soil for tuberculosis, their welfare should receive consideration to a degree only a little less than that accorded to the known contact cases.

The children classified as "Suspects" represent those who reacted to the tuberculin test, but did not have enough of the cardinal points necessary for a positive diagnosis. In this group were placed 12.8 per cent of the children examined.

EVIDENCE OF TUBERCULOUS DISEASE

In table 4 is an analysis of the cases of tuberculous disease shown in 11,449 children examined. There were 553 cases of hilum tuberculosis, or 4.8 per cent of those examined. Of these cases, 2 per cent were five years old, 5 per cent were ten years old, and 6 per cent were fifteen years old. A little over one-third were considered latent, as there were no symptoms of active disease, but the X-ray showed marked evidence of tracheobronchial lymph-node involvement, with calcification and partially calcified primary lesions in the parenchyma.

The percentage of hilum cases found in the contacts was 14.3, and in the noncontacts 3.2. This indicates that frequent and massive infection produces more manifest changes in the hilum region, and more of the contact cases show a primary lesion in the parenchyma.

Pulmonary Disease: One case in every 327 was found to have the adult type of pulmonary disease. Those with simple primary lesions were not included in the pulmonary cases, nor were those that appeared to have small areas of infiltration about the lymph nodes at the root of the lung, when this infiltration did not extend beyond the hilum zone. Only those having definite evidence of infiltration, as shown by mottling and fibrosis in the parenchyma, were classified as having pulmonary tuberculosis.

At ages 14 and 15, the case-rate becomes approximately 1 per cent of the cases examined. The percentage of females in the total number

examined having pulmonary tuberculosis was four times that of the males. This percentage remained practically the same in both the contact and noncontact groups. Only one of these 26 pulmonary cases was found in a rural community. In this connection, it is well to recall that the death-rate among girls in the age-group, 10–19, in Massachusetts is twice that of boys.

According to age, the pulmonary cases were grouped as follows:

AGE	NUMBER	NUMBER OF CHILDREN EXAMINED
7	4	813
8	2	1,066
10	2	1,090
11	1	1,192
12	6	1,171
13	3	920
14	6	587
15	2	290

CONCLUSIONS

Our experience shows that an occasional case of pulmonary tuberculosis may be found in children at any age above five years, but not until the age of fourteen does its incidence equal 1 per cent of the children examined. Also, the X-ray evidence indicates that some of the cases of pulmonary disease in children extend from the hilum or from a partially calcified, primary focus in the parenchyma of the lung.

In finding these cases, one cannot depend very much on the usual examination of the chest, as the physical signs in hilum tuberculosis are slight and inconclusive and often absent; again, in pulmonary tuberculosis in children râles are seldom found, except in advanced disease. The physical examination of the chest in children is of less importance than in adults; and, when râles are found in a child's chest, they are almost always due to some other condition than tuberculosis.

In case-finding, therefore, one should do the cutaneous or intracutaneous test in all children, and then X-ray all the reactors. By so doing, the latent, as well as the active cases, will be brought to light. It is of equal importance to find the latent cases in children, because their latency is only relative, as not enough time can have elapsed to thoroughly fibrose and calcify the foci of disease, and reactivation may occur at any time

THE SIGNIFICANCE OF COUGH DROPLETS AND DRY DUST IN THE SPREAD OF TUBERCULOSIS[1]

F. NEUFELD[2]

Two questions of extreme importance with regard to the spread of tuberculosis have long been discussed: first, whether the infection chiefly takes place from the lungs or from the digestive tract, and second, whether it is the dust carrying the bacteria, or the droplets expectorated by phthisical patients which plays the more important part. As is generally known, Behring, Calmette and others entertained the view that human tuberculosis chiefly takes its origin from infection through the digestive tract. However, this opinion has at present not many followers, in Germany at least. Numerous experiments, especially those of Flügge and his collaborators, came to the conclusion that infection *per os* only succeeds with great difficulty, nearly a million times the number of bacilli being necessary than in the case of pulmonary infection, and from this it followed that the former route could be only of minor importance.

The assertion of Flügge and his followers is, however, true only in a very restricted sense, namely, when the absolutely fatal doses for both ways are compared. Bruno Lange, by continuing the work of Calmette, Griffith and others, has recently investigated the question minutely in a series of experiments with exactly graduated doses down to the lowest limit of effectiveness, and has succeeded in infecting guinea pigs by feeding them with very small doses,—as small as 0.000,01 to 0.000,001 mgm. of tubercle bacilli, that is to say, about 100 bacilli. He found about the same doses active when brought on the mucous membrane of the nose or the conjunctiva.

Without doubt the lungs are relatively well protected against bacterial invasion. By far the greater part of the droplets, as well as of the dust, is deposited on the mucous membranes of the upper respiratory tract, the nose, pharynx, trachea,—especially the larger particles, the chief

[1] Presented before the Pathological Section, at the Twenty-Second Annual Meeting of the National Tuberculosis Association, Washington, D. C., October 5, 1926.

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carriers of bacilli. If we add to this the danger of infection by contact and by food one feels inclined to attribute only little importance to the lungs as ways of entrance of tubercle bacilli. This view, however, has been refuted by careful researches on pulmonary infection, for which we are indebted particularly to Flügge and to Chaussé. Their work was completed by recent experiments carried out in our institute by Lange. Since these investigations, as I believe, are not yet generally known, I wish to discuss them in some detail.

A first series of experiments was conducted in such a manner that a number of guinea pigs were placed in a glass case and made to inhale vaporized tubercle bacilli. Some of the animals were killed immediately afterward, and the entire lung was cut into small pieces with scissors and ground in a mortar. Measured quantities of this mass were injected into healthy animals, and thus it was possible to calculate how many bacilli had entered the lungs. (In this connection I wish to point out that, after numerous experiments with other bacteria and especially with spores, this method, when animals at the same time inhaled in our experimenting room, furnished sufficiently exact and uniform results.) The remaining animals, exposed to the infection, were killed after several weeks, and it was then observed that on an average they showed nearly as many primary tuberculous foci as the number of bacilli they were computed to have inhaled.

This calculation was checked by another method, whereby a good corroboration was obtained. The number of tubercle bacilli present in one litre of air in the inhalation case was determined. As a guinea pig inhales about one-third of a litre of air per minute, and as from previous experiments it was known to us what portion of the germs suspended in the air under such conditions enter the lungs, it was concluded how many bacilli were likely to have invaded the lungs. This calculation corresponded pretty well with the former. I need hardly add that in calculations of this kind there is never to be expected a mathematical conformity but only an approximate one.

Finally, these experiments were completed by tracheal injections with weighed quantities of tubercle bacilli, and for a control it was ascertained by culture how many living germs were contained in the injected fluid. By inoculating one drop of highly diluted suspensions of tubercle bacilli on a medium as prescribed by Levinthal (equal parts of yolk of egg and ox-serum mixed and allowed to congeal slowly in test tubes) one can get

well isolated and easily countable colonies. The limit down to which single colonies of bacilli could be obtained in this way varied somewhat according to the strain and the age of the culture; generally, it was approximately one ten-millionth to one hundred-millionth of a milligram. And this was also the limit to which tracheal infection and likewise subcutaneous, peritoneal and intravenous injections of guinea pigs still succeeded. From all of these investigations we may assume that a single living and virulent bacillus is sufficient to infect a guinea pig in the lung.

According to this, the doses active by inhalation are distinctly smaller than those effective by feeding. There is, however, another difference which is even more important. The entrance of bacilli into the lungs is followed by an acute generalization in every guinea pig, while after feeding (except with enormous doses, such as are never met with practically) only a small percentage of the animals get infected, and of these a good many show a remarkably slow and mild course of the disease, which even sometimes comes to a complete standstill. Thus, in contrast to the pulmonary infection one observes a high constitutional resistance to the infection by all other natural ways. This is also seen in the pathological picture; while inhalation of tubercle bacilli always leads to a primary tuberculous focus in the lungs, the bacilli very often pass through the other mucous membranes without leaving any trace.

Experience tends to prove that in human beings also there is a fundamental difference between the direct infection through the lung and that through all other mucous membranes. Also, in man, a typical primary focus (the Parrot-Küss *Primary Complex*) regularly appears only in the lungs, while the bacilli generally seem to pass through the other mucous membranes such as those of the pharynx, intestines and nose, without leaving any trace. And in man, as well as in the guinea pig, infections by the latter way are usually of an essentially milder nature than pulmonary infections.

How often human beings are naturally infected with tubercle bacilli through the lungs and, on the other hand, by any other avenue, is, I think, difficult to decide. It can, however, hardly be doubted that infection by the latter routes, especially in children, is very frequent. Thus, I believe that in the case of human tuberculosis direct infection through inhalation is by far the most important because it is the most severe; not, as it was formerly believed, because it is the most frequent kind of infection.

Hence, the question as to the part played in pulmonary infections by dry dust and by moist droplets gains renewed interest. It is known that Koch (and before him Villemin), saw the chief source of infection in dried and vaporized sputum, and that Cornet gave support to this opinion by numerous experiments. However, Flügge has disputed the validity of these proofs, and with his collaborators has brought forward much evidence that the moist particles expectorated by phthisical individuals are the most dangerous carriers of the disease. This opinion has been almost generally accepted in Germany, and to the best of my knowledge also in other countries. So, for instance, Hamburger estimated that about 95 per cent of all tuberculous infections were due to droplets. But recently Flügge's conclusions have been again disputed after careful investigations in France by Chaussé, in our country by Bruno Lange. The fact that infection by inhalation succeeds so easily in the experiment is due to the use of the spraying apparatus of Buchner, which produces numerous very minute drops no larger than 2 to 20μ, that is, below 0.02 mm. Such minute drops indeed easily penetrate to the alveoli, and remain suspended in the air for a long time on account of their very small weight; thus, they fulfil the conditions necessary for pulmonary infection. A proof of this is that in experiment they easily pass through spirally bent glass tubes in the shape of an extremely fine mist. But it must be remembered that droplets of such tiny dimensions are very seldom expectorated by patients; according to numerous measurements, the size of the drops usually expectorated varies between 100 and 500μ, that is, 0.1 to 0.5 mm. Drops of this size settle pretty quickly, and are unable to pass the glass tubes mentioned, being deposited on the walls of the tubes. From this it appears that by far the greater number of expectorated drops are incapable of penetrating into the alveoli. For the same reasons it proves to be difficult to infect guinea pigs directly from coughing patients, such experiments being successful only when the animals were coughed at by tuberculous patients for a long time and at a short distance. Neither is every individual coughing and discharging tubercle bacilli able to infect the animals.

The infections obtained in this way, as far as they have been minutely described, do not even always originate from the lungs, but apparently often from the pharynx or the nose, where the coarse sputum droplets, too heavy to reach the lungs, are intercepted.

It has often been pointed out that infection by inhalation must be a

very frequent and a rather easy way, because so many other diseases were spread in this way; for instance, influenza, scarlet fever, measles, meningitis, etc. But this argument is not conclusive. It may be that these diseases are spread by moist droplets, but in some of them it is certain, and in some others it is at least very likely that the infection takes place not through the lungs but through the pharynx. So these other diseases cannot be cited as a proof that droplets may easily penetrate into the lungs.

The observations cited seem to show that expectorated sputum droplets are not so easily capable of penetrating into the lungs as Flügge and his collaborators assumed. On the other hand, it has been proved by the splendid experiments of Chaussé, as well as by recent investigations of Lange, that dry dust is far more dangerous than Flügge thought it to be. It is established that fine dust containing living and virulent bacilli may penetrate nearly as easily into the alveoli as the smallest droplets, and that such dust, which is capable of floating in the air for a long time, may be formed partly from small particles of sputum and partly from dried cough-droplets. It is true that, if such materials are allowed to settle and dry on smooth surfaces, such as slides, hardly any small particles capable of floating in the air develop from them. But the result is essentially different when, as is often the case under natural conditions, the sputum is allowed to dry in a thin layer on pocket handkerchiefs or wool stuffs, or when clothes are polluted with minute droplets. If such objects are afterward shaken, numerous particles of dust, containing bacilli, fly into the air, no matter whether the objects were infected a few hours or a few days previously, or only quite recently. Indeed, it has been proved that, on shaking polluted linen a few seconds after infection, great quantities of bacilli may spread in the air.

The manner in which these bacilli are spread has been closely investigated. Handkerchiefs and woolen rags, which had previously been sprayed with *prodigiosus* bacilli, were shaken out and the dust allowed to settle on slides which were covered with a thin film of agar. These little agar plates were examined under a microscope and then incubated for twenty-four hours. On examination, immediately after the spraying, it was seen that many prodigiosus bacilli lay isolated on the agar surface, and also, when the colonies which had developed were examined, it was found that only about half of them showed a central dust particle. It is, therefore, erroneous to assume that the bacteria, as a rule, cling to small

fibres or dust particles which serve them as carriers. A great part of them are floating freely in the air, and it is easily seen that in this state they are particularly dangerous. If we speak of dust in such cases, this is not quite the correct term. On account of their minute size, particles of this kind float about in the air for a long time. In one instance, there were found about 8 per cent of them in the air one hour after shaking out a handkerchief, which had been soiled with small quantities of sputum.

That the dust which floats about in the air is capable of penetrating into the finest branches of the air-passages with relative ease is sufficiently proved by the experiments of Cornet, Küss and Köhlisch, and especially by the more recent ones of Chaussé. Chaussé allowed guinea pigs to inhale the dust which he obtained by brushing clothes and linen soiled with sputum and dried for some time, or by shaking out handkerchiefs used by phthisical persons. He succeeded in infecting a large number of animals, all of which showed primary foci in the lungs. Lange completely corroborated these results. In one instance he was able to infect all exposed guinea pigs by shaking out a handkerchief, which immediately before had been infected with small quantities of a sputum rich in bacilli; all the animals showed a large number (up to 40) of primary pulmonary foci. This infection was caused by an almost invisible dust.

In further experiments clothes were infected by sprayed droplets similar to the way in which a coughing patient may infect his own clothes and those of his neighbors. These experiments also caused a primary infection of the lungs in about half of the exposed guinea pigs, provided the sputum used was sufficiently rich in bacilli.

From all that has been said here we may assume that, under every-day conditions, small particles of sputum and moist expectoration will often fall on clothes and linen, on beds, upholstery, or on a dusty floor, and that many of them, sooner or later, by the processes of beating, shaking, brushing or sweeping, may get into the air, either in the form of dust or as free bacilli, and thus constitute a great danger for healthy persons and more especially for children who move about in such rooms.

It is easily apparent from these results that our prophylactic measures are thereby made more difficult and need considerable extension.

Lange has gone so far as to conclude that infection by tubercle bacilli in a dry state is by far the most frequent and most important of all modes by which the disease spreads, whereas it is doubtful whether the

direct inhalation of expectorated droplets plays any noticeable rôle in natural infection. It seems remarkable to me that he thus comes back to the standpoint set forth by Robert Koch more than forty years ago in his report on the discovery of the tubercle bacillus. Koch succeeded in infecting guinea pigs with sprayed sputum, but he adds, "We may assume that men who happen to be close by a coughing patient and to inhale freshly expectorated particles of sputum might be infected. This will, however, presumptively not be very often the case because those sputum particles usually are not small enought to float in the air for a longer time. Far more fit for infection is the sputum when dried."

I think we must leave it to further research to decide how frequent there is the opportunity to inhale the germs of tuberculosis, on the one hand in the form of droplets, on the other hand in the form of dust; it being established that they are equally dangerous in both forms, it is our duty to defend ourselves against both.

THE FORMATION OF GIANT CELLS IN TISSUE CULTURES AND THEIR SIMILARITY TO THOSE IN TUBERCULOUS LESIONS[1]

WARREN H. LEWIS[2]

For many years there has been considerable discussion and uncertainty regarding the origin of binucleate cells and giant cells. Two possibilities have presented themselves to the minds of different investigators: one, division of the nucleus without division of the cytoplasm; the other, complete fusion of cells. Studies on fixed and stained tissues can never definitely settle such questions, although they give important clues and suggestions as to the manner in which events occur in the living organism. From an examination of dead material, one might surmise that binucleate and giant cells can arise by division of the nucleus without division of the cytoplasm, by fusion, or by both methods, according to environmental conditions. It is quite evident that only by actual observation on living cells can one settle the question. Tissue or cell cultures afford opportunities for such studies.

The binucleate condition is fairly common in cultures of embryonic mesenchyme, liver, endothelium, ectoderm, endoderm, smooth muscle, heart muscle and kidney epithelium, and of adult mononuclears, macrophages, epithelioid and ectodermal cells. Binucleate cells tend to increase in number with the age of the culture, indicating that the accumulative injurious effects of the abnormal environment may be partly responsible for their formation. Some binucleate cells contain one centrosphere, some two. This suggests that the former may arise by amitotic and the latter by mitotic division of the nucleus or by fusion. I have observed the origin of binucleate cells by both mitotic and amitotic division of the nucleus without division of the cytoplasm. The actual observation of amitotic division of the nucleus is difficult. Macklin was able to follow one division by amitosis, and Lewis and Webster suc-

[1] Presented before the Pathological Section at the twenty-second annual meeting of the National Tuberculosis Association, Washington, D. C., October 6, 1926.

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ceeded in observing the amitotic division of the nucleus without division of the cytoplasm in an epithelioid cell in a culture of human lymph node.

In fixed cultures one frequently encounters, especially in epithelioid cells, nuclei showing all stages, or what appear to be stages, of amitotic division; that is, they show various degrees of splitting; the connection between the two lobes may be reduced to a short slender thread. Such cells are especially abundant in cultures of human lymph nodes (Lewis and Webster, 1921) and seem to indicate that binucleated epithelioid cells and giant cells frequently arise by direct division of the nucleus. When, however, one observes living cells with such nuclei, they usually are seen to revert to the oval form without dividing. It is thus quite evident that the condition of partial or even almost complete cleavage of the nucleus, observed in fixed material, does not mean that the nucleus is dividing by amitosis.

The behavior of the two nuclei in binucleate cells offers some interesting variations. In some cases, as observed by Macklin, the chromatin material from the two may become merged into one equatorial plate of chromosomes; division then proceeds as in the uninuclear cells and results in two independent cells. In others, two equatorial plates of chromosomes are formed, with two spindles and four polar bodies, the division producing four nuclei with or without division of the cytoplasm. It seems probable that when the chromatin material fuses into one plate the binucleate condition is brought about by amitotic division of the nucleus. Occasionally we have observed binucleate cells undergo mitosis when the two spindles had a common pole; one-half the chromatin material from the two spindles united at this pole into a large giant nucleus with double the number of chromosomes, while the two nuclei formed at the opposite poles were of normal size and contained the normal number of chromosomes. Uninuclear giant cells,—that is, cells with one very large nucleus and a large amount of cytoplasm,—are occasionally encountered in cultures and probably arise in the above manner. Those observed were from connective tissue and endothelium.

Multinuclear giant cells have been frequently observed in tissue cultures, especially in the cultures of such organs as the spleen (Lambert, 1912; Lambert and Hanes, 1913; Weil, 1913; Smyth, 1916; Chlopin and Chlopin, 1925; Erdmann, Eisner and Laser, 1925; Timofejewskij and Benewolenskaja, 1925), lymph nodes (Lewis and Webster, 1921; Maximow, 1922, 1924, 1925; Barta, 1925), bone-marrow (Foot, 1912, 1913; Erdmann, 1917; Grossman, 1923), and blood and buffy coat (Awrorow

and Timofejewskij, 1914; M. R. Lewis, 1925; Lewis and Lewis, 1925, 1926; Timofejewskij and Benewolenskaja, 1925), where they seem to arise from the large mononuclears or some of their modifications. Giant cells of connective-tissue origin are rarely seen in cultures and will not be considered here.

Lambert (1912) observed small giant cells in cultures of mouse tumor, and large ones, with three to one hundred nuclei, in cultures of rat spleen, especially in human plasma. These large cells were always spread out in thin sheets on the cover-glass and the nuclei were generally arranged centrally. Lambert was not able to determine their mode of formation, but suggested that the cover-glass might act as a foreign body. He also found giant cells with ten to a hundred or more nuclei in cultures of chick-embryo spleen and intestine. They formed large plasmodial sheets with nuclei scattered irregularly throughout or massed more or less centrally. When lycopodium spores were added to cultures of chick-embryo spleen in plasma, the large mononuclear wandering cells, pulp cells, and endothelial (?) cells collected about the spores after the third day of cultivation and fused to form giant cells. Since the polymorphonuclear leucocytes remained active for only two or three days, Lambert concluded that they probably took no part in the formation of the giant cells. The connective-tissue cells likewise did not appear to take part in their formation, as such cells from cultures of the heart showed no tendency to surround spores and form giant cells.

Lambert and Hanes (1913) observed giant cells with from three to a hundred nuclei in cultures of rat spleen and bone-marrow. These cells were especially numerous when human plasma was used as the culture medium. They moved actively, were highly phagocytic for dead cells and foreign bodies, and tended to spread out widely on the cover-glass.

Weil (1913), working on somewhat similar material, concluded that giant cells were formed by division of the nucleus without division of the cytoplasm. He counted the number of cells that collected about a spore, and found in the fixed material that the giant cell contained more nuclei than could be accounted for by fusion alone.

Smyth (1916) studied cultures of chick spleen with tubercle bacilli and found that the large epithelioid cells, when they came in contact with one another, tended to fuse and form giant cells.

Many of the giant cells found in cultures of spleen and lymph nodes are similar to those found in tuberculous lesions and are of the Langhans type. They are of special interest on that account, and their mode of

origin is of great importance for the understanding of the pathology of tubercles. Lewis and Webster (1921) found such giant cells of frequent occurrence in cultures of normal and tuberculous human lymph nodes in human plasma. The giant cells were characterized by a large granular central area, which varied considerably in size and, in the living cells, had a marked affinity for neutral red, which made the cells conspicuous objects when thus vitally stained. Surrounding this granular central area there was usually an intermediate zone of fat globules. The periphery of the cell consisted of clear cytoplasm, which often extended out into thin membranous pseudopodia when the cell was active. The separate nuclei usually formed a horse-shoe or ring about the granular central area and often were partly or completely embedded in the neighboring zone of fat globules. The mitochondria generally were abundant and distributed between the fat globules and in the clear peripheral zone. These cells are precisely similar in structure to the epithelioid cells and giant cells of tuberculous lesions, and in cultures of normal and of tuberculous lymph nodes one can find a series of such cells containing from one to many nuclei. It would seem an easy task to determine how these giant cells arise from the epithelioid cells in such cultures. Webster and I, however, only after many attempts, succeeded in observing amitotic division of the nucleus without division of the cytoplasm in one epithelioid cell. There were many indications of amitotic division in other epithelioid cells and in the giant cells; so we concluded that the giant cells in such cultures were probably formed by amitotic division of the nucleus without division of the cytoplasm, as we saw no indication of the production of giant cells by fusion. It must be borne in mind, however, that all the cleft nuclei which we followed in living cultures, sometimes for many hours, with the single exception noted, either changed to oval forms or remained undivided.

Maximow (1922, 1924, 1925), in his studies on normal lymphoid tissues and on lymphoid tissues with tubercle bacilli *in vitro*, found that giant cells arose by fusion of the mononuclears, the epithelioid cells, and especially the reticular cells, even when the latter were fixed. His conclusions were based both on fixed material from cultures and on a study of living cells. He looks upon this process of giant-cell formation as a further step in the process of clustering of the cells and of tubercle formation under the influence of a chemical stimulus originating in the bacilli. It must be due, he thinks, to a sudden decrease of surface tension in the respective cell bodies. He sees "no fundamental difference between the

formation of the tuberculous and the common foreign-body giant cells," and the "former are to be looked upon merely as a special type of the latter, acquiring their peculiar character under the influence of some diffusible chemical substance produced by the bacilli." He believes that amitosis plays a very inconspicuous part in the formation of giant cells. The giant cells obtained by him in the cultures with tubercle bacilli do not, however, differ appreciably from those obtained in normal cultures, and cannot be considered as a special type formed under the influence of some diffusible chemical substance from the bacilli. Cultures of tuberculous and normal lymph nodes with tubercle bacilli contain, as a rule, more giant cells than cultures of normal nodes. It would appear, therefore, as though the tubercle bacillus was a factor in increasing their number but not in producing a special type.

Timofejewskij and Benewolenskaja (1925) found many giant cells in cultures of rabbit lung and spleen infected with tubercle bacilli. The cells, variable in size, were spread out on the cover-glass and contained from ten to many nuclei without special arrangement. These investigators think that the tubercle bacilli exert an influence for giant-cell formation, since they are formed for the most part by the fusion of wandering cells about little heaps of tubercle bacilli. They find all stages in their fixed material, just as Maximow did, from clusters of cells with fairly distinct borders to those in which the cell boundaries are completely gone and the cells completely fused together into giant cells. This union of cells was observed many times, apparently in fixed material. The authors state that it is very rare for giant cells to arise by amitosis. We have noted that when cells are clustered their thin boundaries are difficult to distinguish, and that when such clusters are followed for several hours the cells are often seen to migrate apart. It is evident, therefore, that detailed and prolonged observations on living cells are essential to establish firmly the contention that such clusters fuse into giant cells.

Since giant cells are abundant in cultures of the blood and buffy coat, it would seem that here would be an excellent opportunity to determine their mode of formation. Awrorow and Timofejewskij (1914) cultured the buffy coat from leukaemic blood, and found on the fifth day giant cells which they supposed arose by amitotic division of the nuclei, as no fusion was noticed. Timofejewskij and Benewolenskaja (1925) found in cultures of the buffy coat of the blood from the rabbit and dog in plasma, with and without tubercle bacilli, that the wandering cells fused with

one another to form giant cells and large syncytial masses with many nuclei.

Giant cells of the Langhans type form abundantly in cultures of whole blood from various vertebrates (fishes, amphibia, reptiles), and less abundantly in the blood from birds and mammals (M. R. Lewis, 1925; Lewis and Lewis, 1925, 1926). In these blood cultures the large mononuclears hypertrophied and became transformed into typical epithelioid cells, macrophages, intermediate forms and giant cells. We concluded that the monocytes (large mononuclears), epithelioid cells and macrophages were merely different functional states of the same cell-type and that the differences in their appearance were dependent to a large extent on the amount and character of the ingested stuffs, on the degree of digestion of the same, and on the amount of hypertrophy. The similarity of the epithelioid cells and giant cells found in such cultures, and likewise in cultures of lymph nodes and spleen with or without tubercle bacilli, to those found in tubercles can be most adequately demonstrated by comparing living cells stained with neutral red (Lewis, Willis and Lewis). In the blood cultures Mrs. Lewis and I were unable to find evidence of the fusion of cells to form giant cells. We therefore concluded that they probably arose by division of the nucleus without division of the cytoplasm. The evidence for their origin by amitotic division of the nucleus rests on rather slim foundations, namely, the observations of Macklin and of Lewis and Webster, who actually followed in two instances complete cleavage of the nucleus in this manner. These observations are perhaps more than offset, however, by numerous ones where cleft nuclei returned to an oval form. In spite of the fact that many cleft nuclei are to be found, both in living and in fixed cultures, one cannot be certain that they are dividing amitotically. The possibility of giant cells arising by mitotic division of the nucleus has been considered by Mrs. Lewis. She observed in a culture of embryonic-chick lung a giant cell with six spindles become a giant cell with twelve nuclei. This mode of origin of the giant cells in blood cultures, however, seems to be but a remote possibility, for we have never seen a mitotic figure in any of the hundreds of giant cells found there.

During the past year Dr. Brüda and I had the good fortune to study the cultural characteristics of a transmissible spontaneous sarcoma, found by Dr. George Walker in his rat colony in August, 1925. The tumor was diagnosed, both macroscopically and microscopically, as an ordinary spindle-celled sarcoma by the pathologists to whom it was

submitted. Many hundreds of cultures were made, both in autoplasma and in plasma from normal animals, but only one type of cell was found in them, namely, an epithelioid modification of the mononuclear blood cell, which we consider to be the tumor cell. These cells assumed a great variety of forms as they migrated out into the clot or spread out on the cover-glass. They were linear, thread-like or spindle-shaped, multipolar, oval, round and thin, or spherical. At first glance the spindle and multipolar forms might readily be mistaken for connective-tissue cells and did resemble them superficially. The cells were continually changing form; oval cells became multipolar and spindle-like, and changed back to oval or rounded forms. All the forms were characterized by the presence of film-like pseudopodia at the ends of the processes or on the body of the cell,—pseudopodia precisely like those found on the mononuclear blood cells, epithelioid cells and macrophages.

With neutral red and janus green the likeness of these tumor cells to the mononuclear-epithelioid cells of blood cultures and tuberculous lesions was very striking. They all had or acquired the characteristic granular central area, which stained with neutral red, an eccentrically placed nucleus, and a peripheral clear zone in which were short rod and granular mitochrondria. There was often an intermediate zone of small fat globules. In some of the cultures that were made by replanting the explant a second or third time in normal plasma there developed many giant cells of the Langhans type. These cells were highly characteristic and were similar to those that develop from the mononuclear-epithelioid cells in blood cultures and in tuberculous lesions. In the tumor cultures the fusion of the epithelioid cells and giant cells was actually followed from minute to minute. The fusion and complete incorporation of a single cell into a giant cell can take place in fifteen minutes. During this time the nucleus of the newly incorporated cells passes from the periphery to the nuclear region of the giant cell; the granular central area, the intermediate zone of fat globules, and the clear peripheral zone of the mononuclear cell join those of the giant cell (figure 1). When the fusion is completed there is no indication of the place where the cells fused. Giant cells also fused with giant cells to form large masses. During the process of fusion of giant cells with one another the nuclei were often considerably scattered, but as the process neared completion the single giant cell showed no indication of its origin from two masses.

Relatively few of the cells in such cultures fuse, in spite of the fact that they often come in contact with one another and with giant cells. In

one 8-hour culture a small giant cell containing three nuclei was surrounded by numerous epithelioid cells which were in contact with it but which showed no sign of fusing (figure 1). As it slowly migrated, its thin edge came into contact with four cells in succession, and within a period of two hours these had all become completely fused, while other cells which were in contact with it retained their complete independence.

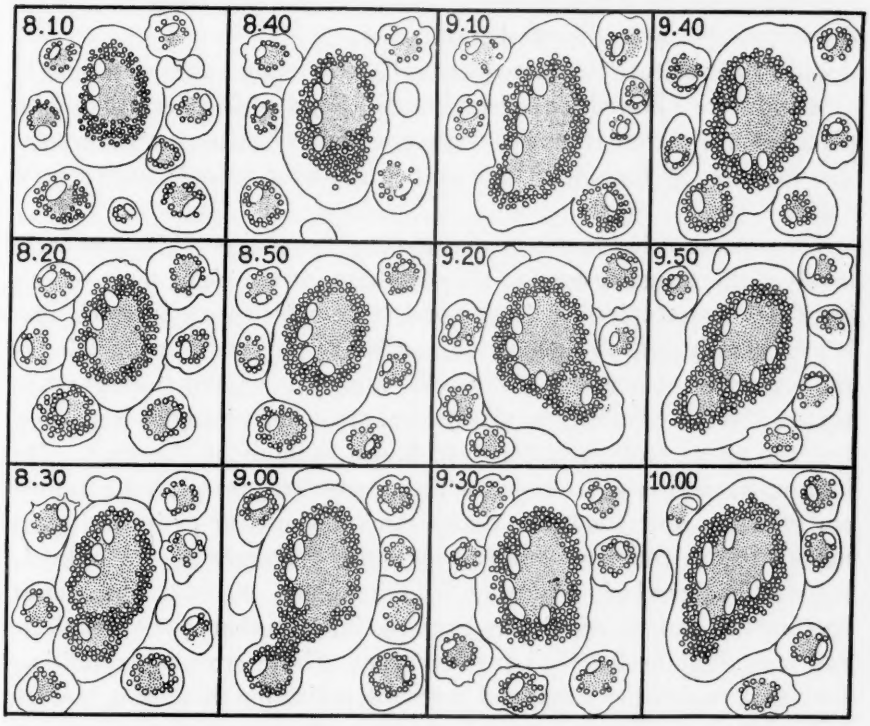

FIG. 1. VARIOUS STAGES IN THE FUSION OF FOUR MONONUCLEAR-EPITHELIOID CELLS WITH A SMALL GIANT CELL

Free-hand semidiagrammatic drawings from a living culture during a period of two hours, 8 to 10 hour culture, second replantation, Walker sarcoma I. × about 300 diameters.

It is evident that the cells must be in a peculiar condition in order that fusion may take place and that this condition is independent of the immediate environment. The idea expressed by Barta, that giant-cell formation is dependent upon low oxygen content, does not hold in all of these cultures, as the plasma is often less than 0.2 mm. in thickness. In the cultures described above, where four cells were seen to fuse with the small giant cell, the plasma was partly liquefied and only about 0.15

mm. in thickness. The cells observed were on the cover-glass. During this same two-hour period seven other giant cells were followed in the eight-hour culture. The nuclei in a second small giant cell increased in number from four to ten; in a third, from five to six; and then these two fused to form a giant cell with sixteen nuclei. In a fourth the nuclei increased from three to four, in a fifth from three to five, and these united into a large cell with nine nuclei. The other three cells observed did not show any increase in the number of nuclei.

In another culture two large giant cells with many nuclei were seen to fuse and were followed for several hours. For a while after fusion took place the nuclei were irregularly scattered, but when the rearrangement was complete all the nuclei were in a circle about a single large central area.

The process of fusion can be divided into two stages. The first stage involves the actual fusion, at the periphery, of the clear, more or less homogeneous ectoplasm. The second stage, which may be much prolonged or only partially completed, consists of the gradual assembling of the respective regions of the two cells into common and united zones; that is, the two or more granular central areas unite into one large area, and the nuclei move or are moved into a zone about this area. The intermediate zones of fat globules, if the latter are present, unite to form one common zone about the central area. The clear peripheral zones unite into one common zone and form the periphery of the cell. In preparations in which this fusion is taking place, and in fixed material, one finds all sorts of conditions, from the initial fusion to the completed and typical giant cell of the Langhans type. The intermediate conditions show scattered nuclei, single and in groups, indicating that fusion of single cells and giant cells may occur faster than the rearrangement into one complete cell. Some of the large plasmodial masses that are spread out over wide areas of the cover-glass show this intermediate condition.

I have recently observed the amitotic division of the nucleus without division of the cytoplasm in several of the large mononuclear tumor cells in cultures in which giant cells were also forming by fusion. In addition, some of the giant cells seemed to show an increase in the number of nuclei without any signs of fusion, and the fixed specimens frequently contained giant cells with what appeared to be stages of amitotic division of the nucleus. The observations, however, are not completed, and I have not as yet satisfied myself that division of the nucleus without division of the cytoplasm actually occurs in giant cells. They are often so thick that it

is difficult to be absolutely sure that when the first count was made some nuclei may not have escaped detection and appeared later on during the shifting of the cell. The fact that amitosis takes place in the mononuclear cells would indicate, however, that the same process probably goes on in the giant cells. Mitotic figures have not been seen in any of the giant cells, and there seems to be no chance that mitotic division of the nucleus without division of the cytoplasm plays a rôle in their formation. The formation of giant cells in tissue cultures by fusion is well established. The importance of amitotic division of the nucleus in their formation is still, however, an open problem.

With but few exceptions, all the giant cells noted in tissue cultures are from such tissues as the spleen, lymph nodes, bone-marrow, and blood, and are derived from the large mononuclears or monocytes, or from modified mononuclears, that is, epithelioid cells and macrophages (clasmatocytes). Various other names have been given to these modifications of the large mononuclears, such as histiocyte, polyblast, resting wandering cell, reticulum or reticular cell, endothelial cell, endothelial leucocyte, etc. The name that enjoys most favor at the present time seems to be *reticulo-endothelium*. There is some peculiarity about the cells of the mononuclear series, associated with their metabolism and with the consistency of their cytoplasm, that renders them more prone than other types of cells to fuse and form giant cells. They are the most highly phagocytic cells of the body and this, too, is bound up with their special metabolism and cytoplasmic consistency. The general character and structure of the multinuclear giant cells vary tremendously. They may be small, with two or three nuclei, or large, with a hundred or more nuclei. They vary from spherical forms to large, thin plasmodial masses that are flattened out over large areas of the cover-glass. The nuclei may be arranged about the periphery of a central area, variable in size, or may be more or less scattered throughout the mass, singly or in groups. The giant cells of the Langhans type (namely, those with a large central area or cytocentrum) contain, according to Maximow, many centrioles. When the nuclei are scattered, singly or in small groups, the centrioles and granular neutral-red-staining material of the central area are likewise scattered. We do not know whether the number of centrioles or of pairs of centrioles equals the number of nuclei or not.

The factors responsible for giant-cell formation are still but little understood. Lambert's experiments with lycopodium spores and his suggestion that the cover-glass also may act as a foreign body in bringing about

the fusion of cells are in line with the deep-rooted belief that foreign bodies may often cause giant-cell formation; hence the name *foreign-body giant cells*. Just what rôle the foreign bodies play is not known; they may produce an increase in the stickiness of the cells (Loeb) or a decrease in their surface tension (Maximow). The cover-glass cannot be a very important factor, since most of the cells attached to it in cultures do not fuse with one another, even where they are in contact. It is not altogether certain that the lycopodium spores act merely as inert foreign bodies, for they may give off substances that alter the cells collected about them.

Barta (1925) has offered an explanation for giant-cell formation in cultures of lymph nodes, based on deficient oxidation. He utilized plasma drops that varied considerably in thickness. In the regions where the migrating cells were near the air surface the cells remained small, contained but few fat droplets, never fused to form giant cells, and divided by mitosis. In the deeper layers of the drop,—that is, at a distance greater than 0.7 mm. from the air surface,—the cytoplasm of the migrating cells hypertrophied and accumulated fat droplets, the nuclei divided by amitosis without division of the cytoplasm, and cells often fused with one another. This assumption of deficient oxygen supply at depths greater than 0.5 to 0.7 mm. from the surface, and of its supposed etiological bearing upon giant-cell production by either amitosis or fusion is based on the work of Leo Loeb, Loeb and Fleisher, and Burrows. Loeb had observed that foreign bodies tend to produce a softening and stickiness of the ectoplasm of amoebocytes, and that cells some distance from blood vessels show amitotic division presumably due to remoteness from the oxygen supply. Loeb and Fleisher noted the injurious effect on cells in cultures when the oxygen supply is markedly diminished. Burrows found that in solid blood clots, at depths greater than 0.5 to 0.7 mm., the haemoglobin was not transformed into oxyhaemoglobin because of insufficient oxygen.

It is not certain that there is any deficiency of oxygen in the drops over 0.7 mm. in thickness or that deficiency of it is a factor in giant-cell formation, since giant cells do form by fusion in drops less than 0.5 mm. in thickness.

It is apparent that the causes responsible for giant-cell formation are not known. Contact with foreign bodies, substances produced by tubercle bacilli, and deficient oxygen are possible factors. If they are the determining ones, how can one explain the lack of fusion of many cells

that are side by side and in the same environment with the few that do fuse? Those that fuse must be in a peculiar state; they must be different from those that do not fuse. In the case cited above, in which I watched four uninuclear cells fuse, one after another, with a small giant cell, there were several similar cells in contact with the giant cell that did not fuse with it. All the cells were of the same type and much alike. There were slight differences, for no two cells are exactly alike, but one could not predict which cells were going to fuse and which were not. The more important factors were not foreign bodies or deficient oxygen, but probably some internal metabolic condition that affected the whole cell, its interior as well as its surface.

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EXPERIMENTAL TUBERCULOSIS IN RATS ON VARIED DIETS[1]

III. SALT FACTORS

LINDA B. LANGE

In two previous papers (1) (2) the attempt has been recorded to study the effect of the lack of dietary factors on the development of tuberculous lesions. Rats of the hooded or of the albino variety and a bovine strain of tubercle bacillus were used. Protein, salts, carbohydrates indirectly, fats and vitamines (antixerophthalmic, antineuritic and antirachitic) were tested. Of all of the diets only that deficient in salts was associated with any difference in the histological picture. In the control animals on an adequate balanced ration and those on all the other deficient diets the tissue reaction of the host to the bacillus consisted merely in the development of small discrete foci of epithelioid cells in the subcutaneous tissue at the point of inoculation and in the lymph nodes in the line of drainage from that point. These foci contained the bacilli. Gradual and complete disappearance of the bacilli and at the same time of the reactive tissue was a constant finding. In the animals on the salt-deficient diet, however, the tissue reaction to the bacillus was more extensive and diffuse, slower to develop and to disappear, and the bacilli in the lesions far more numerous than in those of the other groups of animals. It was noted at the time that proper controls could not be run, due to the impossibility of obtaining a sufficient number of animals. It was necessary therefore to test the validity of these results. At the same time that this was done the diet was further analyzed for the factor responsible for the apparent effect on the tuberculous process.

EXPERIMENTAL

Five diets were used: (1) the standard adequate control diet; (2) the same without the usual added amount of $CaCO_3$ and NaCl,—the ration associated with the more extensive tissue reaction in our earlier series;

[1] From the Department of Bacteriology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland.

(3) the same, deficient in $CaCO_3$ only; and (4) the same, deficient in NaCl only. Such diets should have demonstrated, first, the validity of the previous observations and, second, the particular factor or factors involved in the causation of such dietary effects. Further, we added, at the suggestion of Dr. E. V. McCollum, (5) the same basic diet with $CaCO_3$ increased to 3 per cent, the highest percentage of calcium which can be metabolized by rats without excess of fat-soluble A, the anti-xerophthalmic vitamine. All diets were prepared by Dr. McCollum's methods.

	1	*2*	*3*	*4*	*5*
Rolled oats	40.0	40.0	40.0	40.0	40.0
Casein	5.0	5.0	5.0	5.0	5.0
Gelatin	5.0	5.0	5.0	5.0	5.0
NaCl	1.0	0.0	1.0	0.0	1.0
$CaCO_3$	1.5	0.0	0.0	1.5	3.0
Dextrin	44.5	47.0	46.0	45.5	43.0
Butter fat	3.0	3.0	3.0	3.0	3.0

Through the courtesy of Dr. Howell the rats were bred for us in the Department of Physiological Hygiene of this School from Wistar Institute stock. They were born during July and August of 1924 and kept on an abundant diet, the sexes separate, until the middle of February, 1925. Although some of the rats were still rather small at this time, the experiment was begun by separating them into five lots of ten each and putting one lot on each of the five diets. Thirty-one days later all the animals were injected with bovine tubercle bacilli. No uninfected controls were included, because past experience had shown this to be unnecessary. Two rats of each lot were killed and examined at intervals of one, two, three, four and six weeks after infection, except as the general scheme was modified somewhat by the death at irregular intervals of 14 out of the 50 rats, of which 8 were autopsied and 6 disappeared, presumably consumed by their cage mates. The weights were recorded at the beginning of the experiment, at the time of infection and at autopsy.

The bacillary emulsion was prepared from a thirteen-day culture of the bovine tubercle bacillus, B1, of the Saranac Laboratory, growing actively on a modified Lubenau medium. Culture material was ground in a glass mortar for 25 minutes and centrifugated at low speed for one-half hour. At the end of this time the supernatant fluid was slightly opalescent, and stained films showed single bacilli, numerous pairs and a few small clumps. This was used in quantities of 0.2 cc. per rat sub-

cutaneously in the right groin. In view of the high resistance of the rat a more accurate determination of the infecting dose and an exact proportioning of the dose to the body weights were deemed unnecessary.

At autopsy the gross appearance of the tissues was carefully observed and blocks were fixed in formol-Zenker solution. Paraffine sections, stained in hematoxylin and eosin, were cut from the inguinal and iliac lymph nodes of the right (infected) side, and of those of the left for comparison, of the tracheobronchial lymph nodes, the spleen, liver, lungs and kidney. Bacillary stains were made of the right inguinal lymph nodes, but no others were indicated after study of these sections.

RESULTS

The weight curves in the control lot showed a general downward tendency after infection, only two rats showing a gain in weight. The animals of group 2 (deficient NaCl and $CaCO_3$) and of group 5 (1 per cent NaCl and 3 per cent $CaCO_3$) showed about the same loss of weight as the control-diet group 1; group 3 (1 per cent NaCl and no added $CaCO_3$) showed three times the loss in weight; group 4 (no added NaCl and 1.5 per cent $CaCO_3$) showed only one-third the loss of the controls. The number of natural deaths (4) was higher in group 4 than in any other group, but the number eaten by cage mates (2) was the same as in group 5, which showed a loss of weight about equal to that of the control lot.

The general appearance of the animals was essentially the same in the five groups. The great majority came to autopsy sleek and well nourished, while the few emaciated animals were equally distributed in the five groups. There were a few cases of the common mucopurulent lung disease in groups 1 and 5. Neither the presence of general emaciation nor of the lung disease had any demonstrable effect on the reaction to the tubercle bacillus. This was practically uniform in all the rats, regardless of their general condition or of their diet.

Gross examination of the tissues revealed slight changes if any. The lymph nodes in the path of infection showed enlargement in a number of cases, but no other gross alteration. The majority of the animals exhibited no gross changes at all. Histologically, there was in no case the diffuse retarded more extensive proliferative reaction previously observed with a salt-deficient diet. Rather, there was in all the animals the more common tissue response in the nodes along the line of lymphatic drainage: a diffuse proliferation of epithelioid cells at one week; a grouping of the proliferated cells into sharp foci in two or three weeks;

and beginning of disintegration and absorption in four to five weeks. Bacillary stains of the right inguinal lymph nodes gave the picture usually seen in such tissues of few tubercle bacilli, whether by the acid-fast or the Gram-Weigert stain, and in no case that of the unusually large numbers observed in the first experiment with the low-salt ration. Other tissues showed no significant changes either on gross or microscopic examination.

It would seem, therefore, that the previous findings were unusual, and that they were not the result of the low-salt diet. Nor do the further variations in the salt deficiency introduced in this series in any way affect the rats' response to the bovine tubercle bacillus.

No light has been thrown on the question of the relation of diet to tuberculous infection by these studies. Evidently, under the conditions of the experiments the resistance of the rat is too high to give anything like a progressive infection which might be susceptible of modification by factors such as those of diet. Whether or not this might be possible, if the host's resistance could be lowered or the virulence of the infecting microörganism heightened, remains an open question.

SUMMARY AND CONCLUSIONS

Five groups of ten rats each were put on diets of different salt content (NaCl and $CaCO_3$), infected with bovine tubercle bacilli, and autopsied at intervals of from one to six weeks. No essential difference in the tissue response to the bacillus was observed as between animals on control diet and on salt-deficient diet. Previous observations that deficiency of salts was associated with an altered tissue response were not corroborated. No constant variation in the gross or histological picture has been demonstrated with any of the deficient diets described in the three reports on this series of experiments.

This work has been made possible by a grant of the Research Committee of the American Medical Association.

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ADDRESS OF THE PRESIDENT[1]

ENVIRONMENTS AND REACTIONS IN TUBERCULOSIS

HENRY SEWALL

The words that follow are addressed solely to the Clinician,—that man or woman, with or without a medical degree, who deals with human beings in their morbid states. And, lest it appear that this limitation restricts my purview to technical jargon, I would premise that my conception of the clinician is as one who, *ipso facto*, by the right of eminent domain may claim admission into the inner circle of every field of activity known to man.

We are told that in ancient Egypt the belief, that the stars in their courses powerfully affected human destiny, was well-nigh universal (1). To-day we are breaking to harness the steeds that bring the dawn, and light is one of the principal agents in our therapeusis.

A Frenchman has lately shown a significant correlation between the eleven-year periodicity of sun-spot maxima and human behavior. Human irritability and hyperaesthesia, as evidenced in political revolutions or postrevolutionary activities, vary in a curve curiously parallel to the kinetic flood of solar energy.

A well-known pathologist, who had made intensive study into the origins of epidemic diseases, has come to the conclusion that such epidemics have cosmic and telluric causes back of the pathogenic germs (2).

The variations in rainfall of two thousand years ago have been surmised by study of the annual growth rings of the great sequoia.

Nothing that the chemist or the physicist is engaged with fails to invade the bailiwick of the clinician, from the electron which is the hope of the one to protoplasm which is the despair of the other. And, when he considers Nature's most exalted product, the human being in all its aspects, the clinician finds evolution in the making and himself a catalyst of potent influence.

[1] Delivered at the twenty-third annual meeting of the National Tuberculosis Association, Indianapolis, Indiana, May 23, 1927.

His ideal of self development is poise, a judicial attitude, unabashed by difficulties, unswayed by prejudice. Though certain of final defeat, he never yields in the struggle to defer it. No social caste deceives him as to the essential identity of human materials; his functions cover alike the life of the hovel and of the palace; of the brothel and of the sanctuary; always learning, ever helping, to the end that people may live longer and be happier; and, when he passes, his estate often yields no more than the tribute which Shakespeare brought from the lips of Marc Antony, when, after the battle, he stood by the body of Brutus:

> His life was gentle, and the elements
> So mixed in him that Nature might stand up
> And say to all the world, "This was a man!"

To the clinician who, to paraphrase Oliver Wendell Holmes, is wont to treat with remedies, of which he knows little, human bodies of which he knows less, it is especially worth while to realize the two-edged nature of his weapon.

With catholic clinical audacity I will venture into foreign fields and call attention to what seems to me to be a principle of evolution which first interested me forty-four years ago, but which, so far as I know, has escaped the attention of evolutionists (3). I have a savory memory of the winter of '79, when it was my privilege to use a table in the laboratory of the great physiologist, Carl Ludwig. Those were the salad days of the doctrine of evolution.

Once, when discussing with the Professor the origin of some function, I ventured to use the phrase, "the experiments of Nature," when with almost heated vehemence he interrupted with the retort, in effect, "Nature makes no experiments at all."

The incident is recalled to emphasize my present viewpoint that Nature never ceases to experiment by a process of trial and error, much as does the investigator in his laboratory, and that all her products are rough with the uncleaned shoes of every slough she has traversed.

My meaning will be clearer through induction from specific examples rather than deduction from general principles.

Thus, when we consider the human eye, which has been built up so slowly round the splotch of light-sensitive pigment with which it probably started, we view an instrument astonishingly analogous to the camera of the photographer.

But behold, this camera of Nature leaks light through its sides, an

impossible defect for the physical instrument. Now note this,—that light which has penetrated the sclerotic and choroid coats of the eye is diffused and does not dull the sharpness of the image cast by light entering the pupil. Moreover, these leaking rays are colored red by the blood through which they filter. We know that every color of the spectrum fatigues the retina for itself but enhances its sensibility for its complementary. The complementary color of red is green; the result is that when the eyeball leaks light the green elements of the retina are ever fresh. Need I add that thus Nature's green woos our souls and rests the eye? Again, experiment has shown that of all colors under which objects may be viewed, green is that (even superior to white light) through which minute details of structure may be best perceived. Make your own conclusion.

Once more, when our ancestral eyes shifted from the sides of the head to the front a new difficulty was introduced in the way of securing clarity of vision; for it became physically impossible for the two retinal images to agree exactly when one eye sees more of the right and the other of the left side of an object. There is a measurable discrepancy in the images which fall on corresponding points of the two retinas. But behold again, the Mind, for whose use the eye is made, discounts the minute differences in the retinal images and, moreover, draws out of those very differences a new intellectual perception, a sense perception of the third dimension of space; through which we apprehend depth and solid form,—according to the philospoher, Kant, the highest of all our sense perceptions.

By this example we see that Nature, in her plodding way toward her goal, when encountering a potential enemy among her own laws converts that enemy and acquires new powers that greatly enhance her original endeavor.

So in human history a conquering invader assimilates a hostile people and gains thereby a virility unknown before. Or, from another point of view, it is as if in the smelting of a desired metal the by-products prove more valuable than the substance sought.

That you may not think this merely a fanciful harangue I would refer you to a principle of immunology in which is focused the thought and effort of modern medicine as regards infectious disease.

For reasons that the chemist has failed to reveal, so called "foreign proteins" are poisonous to the normal body. Such a clashing of interests must have been long since fatal to the scheme of evolution had not the Master Workman, be he Personality or Energy, adapted adversity to

his uses. Thus was born Immunity, which, in fancy, bears to the untilled physical field a relation similar to virtue as opposed to innocence in the moral sphere.

And when this foreign protein is reproductive—as in the case of bacteria—old Nature was put to it to protect her favorite child with allergy, with antibodies, and what-not.

I suspect that some such notions must have pervaded the mind of Koch, when he grasped the specific significance of tuberculin toward the disease which gives it being. And the disasters that marked its early application came out of the lack of perception that in immunology quantitative variations in the antigen may produce qualitative differences in tissue behavior.

For eons Nature had conserved her offspring by the application of that principle.

In the early days of tuberculin therapy I asked an able hospital colleague from the surgical staff to advise on a lesion affecting the leg of a patient. At my next visit I found that my consultant had, apparently correctly, diagnosed the trouble but had prescribed for treatment injections of tuberculin in large doses. If he had inquired, or had examined the lungs, he might have found that the patient was suffering from active pulmonary tuberculosis.

This is a practical dilemma which in kind confronts us every day.

I trust my drift may not be too obscure; I am trying to show that in Nature, as in man himself, all great powers are so mingled with what, for our uses, are good or bad that only the alert attention and trained judgment can recognize and separate the one from the other; that we must expand beyond monocular vision into a space of three dimensions.

Dealing, as he must, with agents no man understands, the clinician from the dawn of history has been safeguarded by the development of a faculty of caution for which the most appropriate term that occurs is *Wisdom.*

It is important to enquire whether there is not some objective evidence on which Wisdom may found its conclusions. Decidedly yes;—a change in behavior, which the chemist, mixing fluids in a test-tube, calls *Reaction.*

No empty term this; it is the richest word in the medical vocabulary.

In the days when typhoid fever was our principal acute infection no treatment was so efficacious as the correct application of cold water to the skin. The object of the procedure was not so much the abstraction of heat by conduction as to stir up the poisoned tissues to a salutary reaction.

It is the reaction in his patient which guides the hydrotherapist in his choice of the (generally lamentably neglected) means he uses for restoration.

When we consider that the eye is differentiated to react to but a tiny strip of radiant energy, conditioned by wave-length and frequency of vibration, out of a physically similar congeries of oscillations varying progressively from a wave-length of one-billionth of a centimetre at one extreme, in X-rays, to infinity at the other, in static electricity (4), our minds may well surmise that visual perception by no means limits the biological influence of radiant energy.

Indeed, to-day the radiotherapeutist, who tries to interpret the conundrum of nature's oracle, realizes full well that *Reaction* is the safest guide for his daily ministrations.

Now, by this somewhat tortuous path we are led to consider the spatial distribution of the forces that concern us. I trust you all have in mind those stimulating and instructive essays of Allen Krause on *Environment and Resistance in Tuberculosis* (5). I would be even more emphatic than he in differentiating environment into two factors, the *external* and the *internal*.

The external environment embraces all those agencies which operate on the surface of the body, including the alimentary canal. For our purposes these may be identified under the name of *Climate*, though it would be much more useful for us to deal with its independent variable known as *Weather*.

The internal environment may be conveniently reduced to the medium in which the tissues live, the lymph, together with the energies that activate protoplasm.

My thesis is that through the regulation of the *Environments*[2] we achieve those purposes which are the highest reason for our existence.

All that I have tried to say, and far more, is epitomized in our daily experience with the great disease we are seeking to understand and to control—*Tuberculosis*.

[2] After the above was in press the author found, in J. S. Haldane's volume on *Respiration* (Yale University Press, 1922, p. 383), a discussion of the uniformity of the internal environment, and reference to Claude Bernard's original elaboration of the distinctions between the external and internal environments, which occurs in his *Phénomenès de la vie*, 1885, under the title, *Vie constante on libre*, vol. I, p. 112.

From this the humoralist might be tempted to derive a general definition of disease as a departure from the established uniformity of the internal environment.

How illuminating is its history! Compare its mortality-rate of three generations ago with that of to-day. Compare the apprehension with which it was then regarded with the calm purposeful handling now in use. We cannot but grant that these changes have been wrought by the application of facts wrested from nature by investigation.

It was only in the yesterday of 1840 that the Englishman, George Bodington, first grasped the importance to the consumptive of an environment of the open air, in winter as well as in summer. That his remarkable results were obtained with a simultaneous output of physical exercise by patients that we to-day would consider hazardous need not obscure the beneficent demonstration that the chilling consumptive fares best, not by huddling over the fire in a closed room, but by cultivating reactions to everchanging stimuli which are seldom found within doors.

Bodington put to demonstration the teachings of the ancient Greeks, who must in turn have learned from others, that climate and weather are potent in their uses for restoring the body afflicted with consumption.

Then, rather suddenly, within the memory of most of us, the mental development of our cult turned from an exclusive appreciation of the external environment to a too narrow exaltation of the internal environment.

It was realized that the condition of the patient as regards the "activity" of his disease fundamentally altered his pathological aspect.

It was found that physical and mental rest of a patient, prolonged indefinitely for their effect, could secure arrest of disease with something approaching mathematical accuracy, while overexercise, on the contrary, was as prone to excite it.

There was developed, with the same idea, the surgical procedure of artificial pneumothorax to secure relative quiescence of the more diseased lung.

Let it be noted that all this concerns regulation of the internal environment through controlled metabolism.

Our attention has thus been focused on the salutary but empirical effects of *Rest* without in the least understanding how or why it achieves our purpose; we are beginning, perhaps, to lose memory of the beautiful teachings of Marcus Paterson on the uses of graduated exercise (6).

The explanation of our clinical results must come from the experimentalist who studies the strategy and tactics of two opposing armies, our own body-cells on the one hand and the invading host of tubercle bacilli on the other.

A definite advance seems to have been made by Novy's demonstration of the greed for oxygen manifested by the bacillus (7), which, Corper and Lurie have thought, may regulate the organic implantation of disease following intravenous inoculation (8).

It would be curious if, as Corper suspects, carbon dioxide acts on the bacillus as a respiratory stimulus, as it does, though in a more complicated way, in man.

You will pardon the enthusiasm which suggests that a fundamental problem for the clinician may be the determination of the respective respiratory threshholds of the tissue-cells and of the bacillus. If the cell can function at a lower oxygen tension than the germ we should be able to reduce the microbe to coma if not to actual asphyxia.

But a fundamental and indisputable physiological attribute of *Rest* pertains to the field of mechanics. The surgeon who deals with local infections is meticulous in the care he uses to avoid motion of the affected member. We cannot pause here to demonstrate the tremendous acceleration of the circulation and of the transport of materials of the internal environment through slight muscular movements. Perhaps it is enough for us practical clinicians to realize that our patients do best when we are keen to apprehend their resultant reactions to the combined environments, external and internal.

For my own part, I am impressed with the importance of instructing patients as to what is their sensory norm under environments which experience shows to be conservative of health. In other words, to teach the patient to feel miserable when the environment is not right, as regards, for example, the temperature and the motion of the surrounding air. I will withdraw from this tempting field of hygiene after expressing the suspicion that that degree of temperature is most salutary for sick or well which is the lowest in which the body can be maintained in comfort.

Be it said to his shame, the average healthy doctor is apparently one of those least fitted to instinctively appreciate these relations. Even when he feels the environment to be wrong his training in self-repression is apt to subdue his manifestations of discomfort.

Consider the meeting-rooms of medical societies; would that some sprite were always present to note the curves of air-movement, its temperature and chemical composition!

And in our hospitals, those resorts which we labor so hard to provide with every artificial aid to restore the sick, how often must the votary of Nature's therapeutics rage to find in them a dead air, heated in winter to a temperature of 75 to 80 or more degrees Fahrenheit!

You may pardon me, in closing, if I revert to what appears to be a clinical demonstration, in mass, of the respective biological influence of the external and internal environments upon persons afflicted with tuberculosis.

No apology is offered for referring to my adopted State, Colorado, as a health resort. Until recently, for more than half a century it had been a veritable Mecca for sufferers with tuberculosis of the lungs, and to-day a very large proportion of its active and useful citizens is composed of those who have there recovered health.

Yet the mortality statistics of the Census Bureau constantly charge Colorado with about the highest death-rate from tuberculosis of all States in the Union.

A few years ago a Committee of the Denver Sanatorium Association undertook an investigation to determine from available evidence the specific relations of *Climate*, as exhibited in Colorado, to the incidence and course of tuberculosis. The material used in the study was furnished by the mortality reports of the United States Census and from the death certificates filed with the State Board of Health of Colorado (9).

For the thirteen years, 1908–1920, the total number of deaths from tuberculosis in Colorado was 23,608. During the period in question the average annual death-rate for tuberculosis per 100,000 of the population in the whole Registration Area was 147.5; in Colorado it was 208.9.

But the death-rate for Colorado, analyzed according to the place where the disease was developed showed: developed outside Colorado, 150.0; developed inside Colorado, 30.8; place of development unknown, 27.5.

Whereby it appears that the death-rate from tuberculosis indigenous to Colorado is represented by a notably small figure. But the Committee was still confronted with the appalling mortality from exogenous tuberculosis.

Then the thought occurred to analyze the decedence among immigrants according to the duration of their residence in the State.

The interesting result developed that

more than 40 per cent of the deaths from tuberculosis occurring each year in Colorado are in newcomers who have sojourned in the State but one year or less; and of these 9,539 deaths, 50.8 per cent, occurred within the first three months' residence.

When the excessive mortality rate for tuberculosis in Colorado is corrected by the subtraction of deaths occurring within the first year of residence, it is reduced to 123.9 per 100,000 population, as compared with 147.5 per 100,000

for the Registration Area. Subtracting again the death-rate from tuberculosis developed in Colorado, 30.8 per cent per 100,000 population, we have a remainder mortality rate from tuberculosis of 93.1 per 100,000 in a population, a large proportion, if not most, of whose members have or have had tuberculosis. When it is considered that this group contains all the leftovers from the mass of invalids who have survived their first year's residence, we can only conclude that climate may offer an environment peculiarly beneficent to the needs of most tuberculous patients (9).

But still the question looms: *Why* the great mortality rate among consumptives newly arrived in Colorado? There are two demonstrable reasons: first, the group of invalid immigrants is largely composed of patients in a late stage of disease, for whom there is no help.

Second, many who might readily secure arrest of their disease, ill-instructed in the dangers of overexercise, throw away their chances for improvement by yielding to the urge for movement so characteristic in a stimulating climate. But a very large proportion of those who might be helped fall by the wayside through work and worry, for they have no reserve of money capital with which to conduct a cure.

The social aspects of this problem are plain enough.

What interests us here is the demonstration that misuse of the internal environment, through the excitement of a pathological metabolism through overexercise, may far overbalance the salutary influence of the external environment wherever it may be laid.

What I am trying to express is a protest against the tendency among physicians during the last decade or more to minimize or neglect the virtues of the external environment, as manifested in climate, especially during the long period of subsidence in tuberculosis activity.

There is not one of us who has not at times rejoiced in the tingling race of blood set going in us by the frosty air; or our hearts awake when green-sprouting spring starts birds singing, and white fleeces soar in the blue sky.

The Greeks had their Arcadia. We sometimes miss the charm of ours.

The Earthly Paradise is found wherever the forces of nature are most freely offered for the welfare of human life.

It is surely significant that man, born in flesh, is cloyed with repetition of the delights of the flesh.

Only one field of sense knows no exhaustion; it is the feeling of well-being which responds untired to the harmony of a suitable environment.

On the other hand, no laboratory diagnostics will ever be able to sup-

plant the physician's perception of the meaning of reactions which translate to him the tendencies of that vital metabolism which regulates the internal environment.

In conclusion, nothing could better illustrate the functions of this great organization, the National Tuberculosis Association, than the obvious need for mass education of people, who are well, in the general principles of the prophylaxis and treatment of tuberculosis; that through periodical examinations by accredited experts the apparently healthy person can alone get reliable assurance of the absence of impending evil.

To teach people sick with tuberculosis that it is against their interests to leave friends and home in search of health unless with resources sufficient to maintain them at least for a year at rest.

And, for ourselves, there is the task of keeping well-balanced that judgment which is so difficult when called upon to weigh the claims of new products from laboratory or clinic. For many generations our lives are like to end with the question: What *are* the healing powers of Nature?

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THE CONTROL OF TUBERCULOSIS IN FLORENCE[1]

G. B. ROATTA[2]

I

HISTORICAL NOTES

First Antituberculosis Legislation: the Founding of the First Marine Hospital Giuseppe Barellai

In this respect Florence has been a pioneer city, as she has also been the first in the field with regard to the institution of marine hospitals.

As to the question of legislation: in Italy, or indeed, one had better say, in the whole Mediterranean basin, the classical tradition of tuberculous contagion has survived all through the Middle Ages and the Renaissance period, up to the present day, thanks to the teaching of the medical schools. And even when medical science seemed to speak uncertainly, and at times to contradict her own pronouncements, the voice of the people never wavered in this traditional belief.

An eminent English writer has told me how her parents scoffed at the (to them) superstitious fear of the Tuscan peasants, who dreaded infection through contact or contiguity with tuberculosis cases.

Messer Pagolo da Certaldo, in a *Book of Good Customs*, written in the 14th century and unearthed in the State Archives of Florence by A. Corsini, gives the following good advice on that much taught and never sufficiently acquired subject—how to choose a wife: "And see that thou takest not to wife one born of a horde of lunaticks or phthisics . . . . lest it may be that thy children born of her may be imbued with these diseases or infirmities."

The decisive proofs given through the experiments of Villemin, flanked by that of Armanni, did not therefore reveal a new truth to Italy, but supported an already deeply rooted belief.

Considering this mental attitude, it is not to be wondered at if the holders of offices created in Italy to protect the country from plague and

[1] Presented before the Sociological Section at the twenty-second annual meeting of the National Tuberculosis Association, Washington, D. C., October 5, 1926.

[2] Director of Dispensaries, Florence, Italy.

pestilence during the Middle Ages and the Renaissance gave their attention and devoted their activities to the study of the problem of tuberculosis.

In Florence in 1750 the *Magistrato di Sanità* (Magistrate of Health) puts the question to the Florentine Medical College: "What is there of most susceptible to the malignity of tubercular infection, and what provision could be made, or remedies applied, for the disinfection and purification of that which has been used by, or remained in the vicinity of, a person affected by this disease?"

At the same time the *Signori della Sanità di Firenze* (Board of Health) opened an investigation, as we should say to-day in the other States of the country, to know "if there be any law or regulation, controlling the action of the public, which prescribes a line of conduct to be followed, which shall serve to restrict the spreading of consumption." This investigation was extended to the Republic of Venice, the Republic of Lucca, and the Kingdom of Naples. The answer from the Republic of Lucca had undoubtedly a special importance, since in that State, as early as 1699, there existed a series of prophylactic measures, among which we find that notification is required, that disinfection is carried out, both of the effects and of the home of the patient, and that autopsy is authorized in order that the doctors may the better study the nature of the disease. Moreover, at that time the building of a sanatorium was contemplated, as consumptives were not received at the general hospital. This sanatorium was to be erected "at a sufficient distance from the town," and so constructed that the suspect cases should be separated from those whose diagnosis was certain.

This was to apply to men and women alike, and accommodation was to be provided for all those who attended to the sick, well separated from the patients themselves.

Having made these preliminary studies, on the 11th of November, 1754, the *Magistrato di Sanità* issued an *Edict toward the Alleviation of the Consequences of the Disease of Phthisis*, which edict, following the analogous one of the Republic of Lucca, is the first instance of anti-tuberculosis legislation laid down by any European government.

Even to-day we are filled with admiration for so wise and provident an edict, but unfortunately its provisions were observed with considerable laxity, nor were they of long duration.

We must except the Republic of Lucca, where these measures remained in force up to 1799, when they fell into disuse at the time when the proud little republic lost her liberty.

At the beginning of the nineteenth century the sapient and provident measures once in use no longer existed, and indeed were but little remembered. At this time, however, a new initiative sprang up which was destined to bear much fruit, that is, sea-side treatment.

In truth, sea-baths in tubs were given in Pisa long before, and were in use in the surgical clinics and in various city institutions (orphan asylums, seminaries, etc.) as far back as the seventeenth century. We find that these sea-baths were ordered for those suffering from scrofulous affections.

But sea-bathing itself was introduced into Tuscany as a curative measure by Luigi Morelli, M.D., of the University of Pisa, who during a stay in England had become familiar with the sea-bathing establishments first started in that country toward the middle of the eighteenth century.

The sending of the first party of children and invalids to the sea took place on August 10, 1839, at the instance of the Commissary of the Hospital of Pisa, Cav. Chamberlain Luigi Sassetti. But the plan of a marine hospital, where, in addition to the sea-baths and the spending of a certain number of hours on the beach, there should be accommodation suitable for the prolonged and uninterrupted period of residence, was entirely the work of Giuseppe Barellai, House Doctor at the Hospital of S. M. Nuova in Florence.

In 1853 he showed portraits of two children to the *Accademia Fisica Fiorentina*. One of these children had just died; the other was dying in a hospital of mesenteric tuberculosis, and Barellai had caused these portraits to be painted by Stefano Ussi, a well-known artist of the day. In the speech which Barellai made on this occasion he said, "Rather as a philanthropist to philanthropists than as a medical man to medical men, I insist on the fact that pure air and sea-water are the only cure for conditions such as these."

In 1854 a society was formed for the purpose of organizing marine hospitals. In 1856 a marine hospital was in running order, in quarters adapted for the purpose as well as circumstances permitted. And in 1861 we come to the ceremonial laying of the corner stone of the *Ospizio Marino Vittorio Emanuele II*, at Viareggio, which hospital is in use to-day.

Giuseppe Barellai's crusade was felt throughout Italy and beyond the Alps. On hearing of it Michelet writes, "Il y a la un germe de conséquences incalculables et qui peut changer le monde."

In the writings of Barellai on the subject, we find doctrines laid down which only in much later days became a recognized asset of medical knowledge.

As early as 1863, after having premised that "the best Italian medical science has always resented the barbaric, amputative and mutilating form of treatment, which like all evils assails from the outside, and prefers instead to adopt conservative methods as far as possible," he goes on so say: "Now with the founding of marine hospitals this conservative treatment will bear witness to its potency, and by bringing to the notice of the public its curative powers, never before judged possible because never before taken heed of, the dread instruments of the surgeon, too often used in ignorance or for greed of gain, will be arrested in their devastating work."

And yet further: "Hospitals, and especially large hospitals, tend to increase scrofula. And he who in hospital is already scrofulous will become more so, or will die, or will painfully linger on indefinitely. A hospital is a veritable prison for scrofulous children. Let us give them freedom; let us give them the benefit of the life-giving sunlight, and of the pure air of the seaside."

This crusade of Barellai's has been crowned with success, and numerous institutions have come into being throughout Italy not only for prophylactic but for curative treatment. Some are open all the year round; the majority only for the summer months.

II

PRESENT CONDITIONS

Clinics, Homes and Open-Air Schools: Summer Camps (Seaside and Mountain): Day Camp in Cascine Park: Home for the Children of Tuberculous Parents: New Tuberculosis Hospital: Marine Hospital: Maternity: Child Welfare Laws: Public-Health Nurses: Admittance to Hospital

In a book called *The Control and Eradication of Tuberculosis*, published in Edinburgh in 1911, and dedicated to Sir Robert Philip, Dr. G. Sandison Brock has given a very fair account of the antituberculosis campaign in Italy in 1911.

Much has been accomplished since then, and the necessity for this campaign is universally recognized, and is being carried out in ever-increasing measure.

The modern campaign against tuberculosis in Florence was started with a home for contact cases, familiarly known as the *Ulivini*, due to the initiative of Dr. Pieragnoli, and opened in 1902.

Shortly afterward (in 1907) the *Società Umberto I* opened the first tuberculosis clinic, another home for delicate children and contact cases, and an open-air school. The municipality followed this example, and is now providing for three open-air schools. The schools of the town provide four mountain holiday camps for their pupils. Playgrounds do not exist, but arrangements have been made for gymnastics, musical drills, etc., after school hours in school buildings.

Geographically speaking, Florence is fortunately situated. Open to the sea on the West, she is encircled on the other sides by the chains of the Apennines, which at their highest points rise to 5,000 feet. Both sea and mountains are easy of access, and in the summer months large parties of children are sent to one or another of the various marine establishments at Viareggio, Marina di Massa, Marina di Pisa, Leghorn, Quercianella or Antignano, while others go to the mountain camps which are instituted for the benefit of the school children.

Private enterprise assists financially, and the Women Fascists this year are finding the money necessary for 500 children. The expense of each child for a month is covered by 250 lire, which includes the railway journey—approximately 10 dollars. Some 2,000 children spend a month in this way each summer, and possibly the open-air life and the regular food are as beneficial as the change of air.

This is proved to a certain extent by the excellent results given by a day camp in the Cascine, the Public Park of Florence, where 100 children spend the summer in the open air, returning to their homes at night. These children come from the poorer parts of the town, at easy distance from the park, and are among the number who have been crowded out from the advantages of the seaside or the mountains. The expenses of this camp are entirely met by two American ladies residing in Florence, the Misses Buttles of Newport, while the site of the camp is given by the Commune. At the end of the summer the children are found to have all increased in weight and measurements, certainly not less than those who have had their holiday elsewhere. I hope that this experience will show that much can be got by a better use of the air and climate of a town, without depending entirely upon a change of locality and exceptional climates, like those of the seaside and the mountains.

At the end of the war, the American colony, which had financed the American Hospital for Italian wounded, in a 14th-century villa offered for the purpose, turned over to the Italian Red Cross the entire equipment for 100 beds, as well as a considerable sum of money and a radio-

graph plant, to be used as a home for children of tuberculous parents. Circumstances necessitated its temporary closing, but it is now reopened, having been altered and to a certain extent remodernized. Besides 100 children in the main building, the American pavilion (which must retain this name) accommodates babies up to three years of age.

Recently a new tuberculosis clinic has been opened by the Italian Red Cross, with the services of a public-health nurse, and yet another by the initiative of the tuberculous ex-service men; while the San Domenico Free Dispensary provides for the Fiesole district.

Speaking from the experience of the oldest dispensary, I can say that the work is much appreciated by the population, who come spontaneously in increasing numbers to ask advice and to have contact cases examined.

Last year a new hospital for tuberculosis cases was opened outside the town, and provides for 140 beds. It has plenty of air-space, and permits of indefinite expansion, as funds allow. Sanatoria and preventoria are nevertheless insufficient. While indigent patients are received at this hospital, accommodation is wholly insufficient for patients of the middle class. The reason for this is the natural one that the proper treatment requires an outlay not commensurate with what such patients are able to pay.

In hospital, the question of manual work or occupational therapy is undeveloped, as in many cases the patients seem to resent anything of the kind, although my own experience during the war justifies the adoption of some occupation, not only as generally beneficial, but also to some extent remunerative.

The Marine Hospital at Viareggio, of which I have already spoken, still exists in the same building which was opened in 1861. The present capacity is 110 beds for permanent cases of external tuberculosis and 240 beds for predisposed children and contact cases, which are sent there from June to November. Girls are received up to the age of 21, and boys up to the age of 12. A radical change is about to be made, and a new building erected for cases of external tuberculosis, with some provision for pulmonary cases in the initial stage. This will be at some distance from the present building, which will then have a capacity of 400 beds for the seaside-bathing cases, while the new building will be able to receive not only females up to the age of 21, but also adult males, for whom there is now very inadequate provision.

Infants and expectant mothers are assisted by the *Cassa di Previdenza per la Maternità*, which gives a layette and a grant of money to each

mother, who, through her membership fee of 50 centimes a month (3 cents), is entitled to it.

Italian mothers generally nurse their babies, but when that is not possible, as in the case of tuberculous mothers, there are eight *Milk Centres*, which provide specially prepared and sterilized milk, suitable for each individual case, in bottles ready for each feeding.

It will be seen by these few notes that even in the antituberculosis campaign Florence sticks to her old tradition, according to which children play such a conspicuous part in the artistic life of her citizens. The sentiment of the people finds expression in the elevation above her altars of the Holy Child upon His Mother's knee, a symbol of the reverence due to childhood,—in itself so innocent and yet coupled with power. For centuries past, from the facade of the Foundling Hospital of the Innocents, Luca della Robbia's babies have looked with protecting eyes upon the girl mothers who seek its refuge: no longer leaving their babies nameless and abandoned, but nursing and tending them in this sanctuary until necessary arrangements can be made for their future.

Now the new law (December, 1925), which relates largely to child welfare, should be of great assistance. The restrictions on the sale of tobacco and of alcohol, the discontinuing of the supply of wine in boarding schools, and the difficulties put in the way of the employment of young children for trade purposes, should help on the antituberculosis campaign. The increase in the number of school inspectors and of public-health nurses should also be factors in bettering general hygienic conditions.

But the greatest assistance in the antituberculosis campaign in Florence is given by the district or public-health nurses. In my opinion this is the most modern and the most efficient of the antituberculosis institutions of Florence, even if it be not (and perhaps for that very reason) strictly and exclusively antituberculosis. Owing to the conditions of their training and to the small stipend which they receive, it results that the women in Italy who hold the position of *Assistente Sanitaria* are drawn from a class of educated women with some financial background, who embrace a career which at present does not give a living wage, and requires a real spirit of abnegation and a vocation for the work.

Their duties are along the lines laid down for the American public-health nurses; and the Florentine School received its first instruction at the hands of Miss Edna Foley of Chicago, deputed, with several other A. R. Nurses, to spend some months in Florence, and to train a group of war nurses having three years' service to their credit. We now possess a staff of public-health nurses, more or less evenly distributed through the

different quarters of the city, taking their orders from the doctors, following up cases, and obtaining admittance to hospitals, etc.

The last is an important item, as the system of admitting patients to hospital is so different from that in use in the United States that a word concerning it may not be amiss. First-aid cases are always received, in whatever way they arrive at the door of the hospital. But for a period of treatment an indigent patient must produce his or her "certificate of poverty," granted by the *Comune*, and of which there are two kinds,—absolute and temporary.

In any case the fee for residence must be paid, either by the *Comune*, which is responsible for those holding the certificate, or by the patient, from whom a deposit is required. In many cases the public-health nurse is able to be of use. Her knowledge of the people and their circumstances has proved to be so trustworthy, that the *Comune* gives the necessary paper on her representation, investigation having shown that it is always a justified request; naturally she must be backed up by a medical certificate.

The routine duties of her service are such as she carries out in other countries, and especially in tuberculosis cases I cannot too strongly emphasize her value. Up to the present, the expenses of these nurses are met by private committees, which are federated together in a species of League, under a Central Committee. The *Consorzio Antitubercolare*[3] makes a small grant to this Federation, but with that exception funds are provided by private subscription.

III

TUBERCULOSIS MORTALITY IN FLORENCE: STATISTICS

The City of Florence: Statistics Zones: Tuberculosis Mortality in Florence as Compared with the Other Cities of Italy before, during, and after the War: War Tuberculosis,—the Legend and the Reality: Tuberculosis Mortality According to Age: Death-Rate from Tuberculosis According to Sex: Tuberculosis Mortality in Florence and Its Distribution

The *Comune* of Florence occupies an area of 6,271 hectares, of which 4,358 are on the right bank of the Arno, and 1,780 on the left bank, while 132 hectares are occupied by the river itself.

[3] The *Consorzio Antitubercolare* is a Board (there being one in each of the 76 provinces), which receives money—so much per capita—in each province. For the Province of Florence this contribution is 23 centimes (less than one cent) per capita. The funds so collected are distributed among the different antituberculosis institutions of the Province.

The town and part of the surrounding country are on flat ground, at an altitude varying from 40 to 60 metres. The remaining territory is hilly, rising to an altitude of 200 metres on the south, and 300 on the north side.

The greatest length follows the direction of the river (West to East) and reaches 11 kilometres. The greatest breadth (South to North) measures 10.8 kilometres.

Nearly all the territory has an urban character; in the rural zone we find villas, gardens, suburbs and kitchen-gardens.

The inhabitants, except in a few zones, are not overcrowded. This is due partly to the absence of many-storied houses subdivided into numerous flats and also to the presence of numerous gardens, even in the centre of the town. The population in 1911 was 232,860; in 1921, 253,565; and in 1925, 263,845.

There are no large industries; all trades are carried on as in years past, giving employment to a limited number of workmen.

The majority of the population (two-thirds) is represented by clerks, workmen, domestic servants and unskilled laborers, with a prevalence of the latter. All other social groups make up the remainder with a slight prevalence of professional men and artists, and those of undefined condition.

Florence is a residential city, replete with artistic and historical associations, and with a business element sufficient for her own needs, but in which industries play a negligible part.

As far back as 1907 the *Statistics Office*, under the direction of Signor Ugo Giusti, found the administrative divisions of the *Comune* insufficient for demographic studies based on the economic and social character of the population, and he adopted a division of the Comunal territory into *Statistic Zones*, in order the better to set forth the different demographic phenomena. These zones are now 18 in number, 9 of which are inside the old city limits (Centro, Uffizi, S. Croce, Affrico, Viali, S. M. Novella, S. Iacopino, S. Spirito and S. Niccolò) and 9 are outside (S. Salvi, S. Gervasio, Pellegrino, Montughi, Rifredi, Pignone, Ricorboli, Rovezzano-Settignano, and Trespiano-Careggi).

The last two zones mentioned (Rovezzano-Settignano and Trespiano-Careggi) are not included in the plan which follows, drawn up by Signor Giusti, as they were added to the city limits at a later date than his publication *On Tuberculosis in Florence in the Quinquennium 1907–1911.*

The inclusion of these two zones in the statistics would therefore make a comparative study of the tuberculosis mortality impracticable as between

those dates and the years which follow. As it is, these districts are mostly of an agricultural character, and would not influence the tuberculosis statistics of the town.

Statistics of Zones

ZONES	GENERAL FEATURES (SEE PLATE 5)
1. Centro	(Right bank of Arno.) New or largely rebuilt edifices. Wide streets. Many public buildings, hotels, shops.
2. Uffizi	Ancient, even medieval buildings. Narrow streets. Poor and overcrowded dwellings predominate.
3. S. Croce	Old buildings. Narrow streets. Small shops and poor and overcrowded dwellings predominate.
4. Affrico	Modern buildings. Many gardens. Middle class and workmen's houses.
5. Viali	Principally modern houses. Villas and gardens. Wide streets and avenues.
6. S. M. Novella	Many buildings date from medieval times, with an admixture of modern edifices. Streets generally wide and regular. Hotels are found in the modern part, while the older portion is occupied by small shops, and poor houses which are overpopulated.
7. S. Iacopino	Modern buildings. Wide and regular streets. Small houses built for the use of one family alone.
8. S. Spirito	(On the left bank of the Arno.) Buildings of ancient date. Overcrowded dwellings.
9. S. Niccolò	Built on the hillside facing north. Old buildings.
10. S. Salvi	(On the right bank of the Arno.) Largely consists of new buildings. Kitchen-gardens and fields. Some factories.
11. S. Gervasio	On the hillside with southern exposure. New buildings. Wide streets. Villas and gardens.
12. Pellegrino, Lapo	Congested district of old buildings on flat ground with groups of old houses on the hillside. Several large villas and gardens.
13. Montughi *14. Rifredi*	Partly crowded districts with old houses, otherwise modern edifices and some factories.
15. Pignone, Bellosguardo	(On the left bank of the Arno.) The hills are occupied by villas, parks and gardens. The flat ground has workmen's houses, some old buildings, and market-gardens with a working-class population.
16. Ricorboli, Pian dei Giullari	Fairly new buildings. Wide streets and avenues. Villas and parks are found on the hillside, and workmen's houses and middle-class dwellings on the flat.

The homogeneous character of the zones must always be understood to be relative. In Florence, much less than in other cities, do we find districts inhabited solely by a single class, and residential or purely business quarters do not exist.

In the poorest parts of the town, as in S. Spirito, for instance, many old palaces show armorial bearings in narrow and seemingly poor streets,

while in the zone of the *Viali*, or Avenues, we find blocks of artisan dwellings near the many villas with their gardens.

The fine palaces and hotels situated on the river bank are as splendid facades to the poor houses hidden away in the mean streets at the back.

I have thought it advisable to draw a comparison between Florence and the other large cities of Italy (over 100,000 inhabitants) in the three characteristic periods of before, during, and after the war, as regards tuberculosis mortality. By this means we can form a more exact idea of her position in the scale.

This comparison relates to three group-periods of three years each, and in order to make it the more striking we have omitted one year between the first and second triennial period, that is, 1915, when the war had already commenced but its effects were not yet apparent. In the same way, the two years immediately following the war have been omitted, as the conditions were still in existence.

On examining plate 1 it is evident that in regard to other Italian cities Florence has improved her status. While in war time, as well as in the prewar period, only Trieste showed a higher mortality from tuberculosis, in the postwar period she comes fourth in the list, on a par with Turin.

Mortality from Tuberculosis

Prewar Period:	
(Trieste)*	415
Florence	288
Brescia	279
War-time:	
(Trieste)	778
Florence	460
Brescia	412
Postwar Period:	
Trieste	291
Padua	287
Brescia	279
Turin	243
Florence	243
Venice	242

* Trieste, as is well known, returned to Italy only after the battle of Vittorio Veneto, which ended the war on the Italian front.

The charts plainly show the enormous increase in tuberculosis mortality during the war among the whole of the population, male and female. This was due to the privations and to the strenuous work to which the

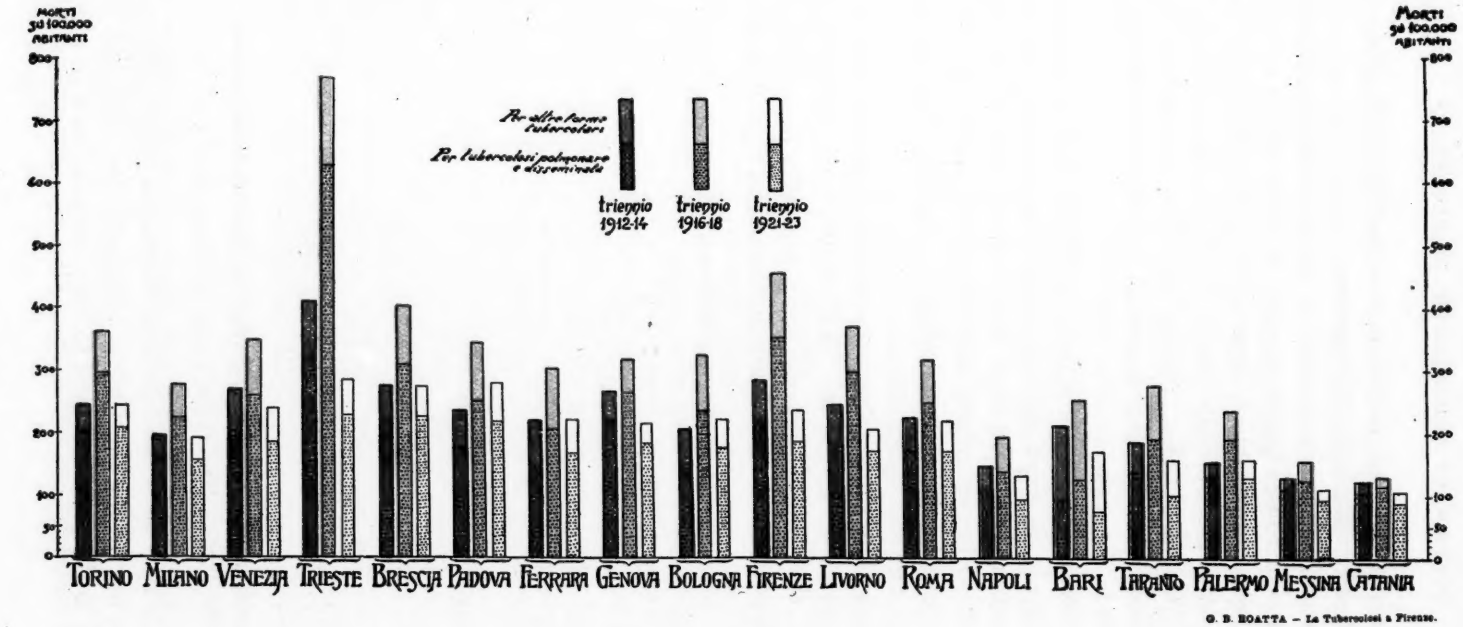


PLATE 1

DEATH-RATES FROM PULMONARY AND DISSEMINATED TUBERCULOSIS AND FROM OTHER FORMS OF TUBERCULOSIS FROM 1912 TO 1923 IN SOME OF THE PRINCIPAL CITIES OF ITALY

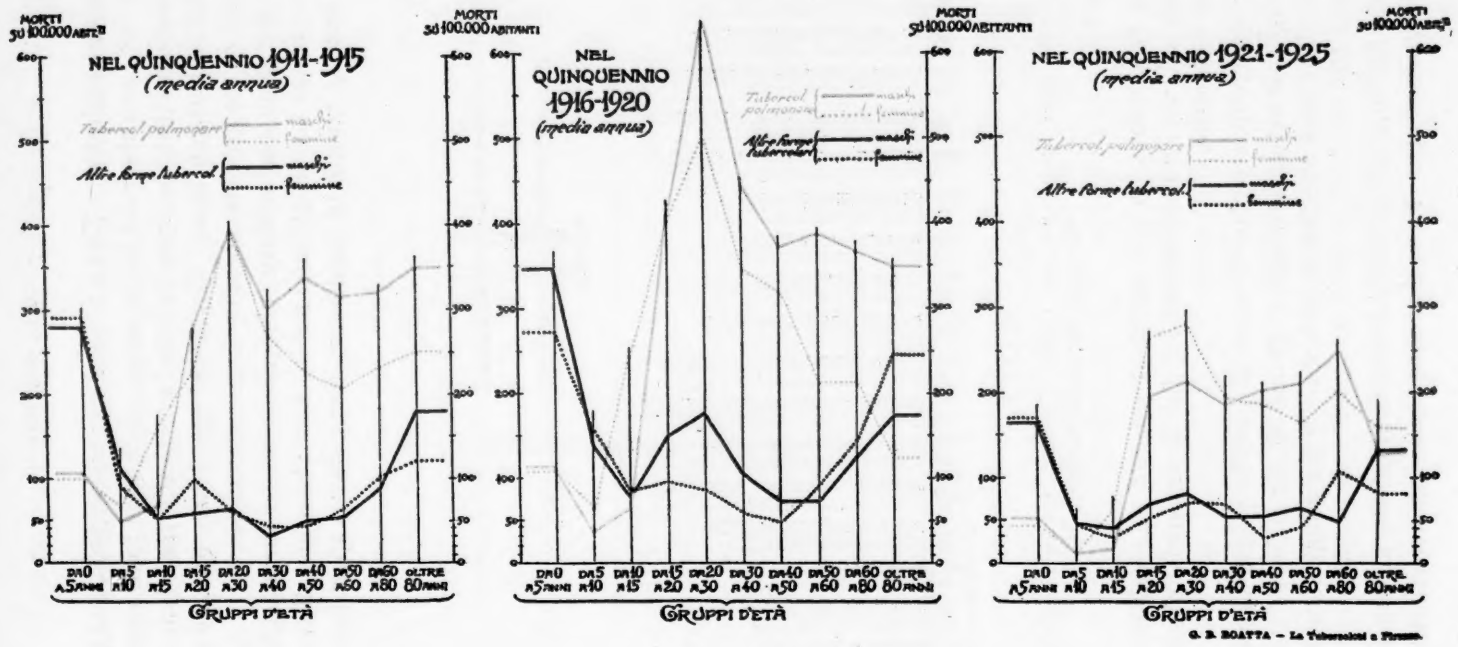


PLATE 2

DEATH-RATES FROM PULMONARY AND OTHER FORMS OF TUBERCULOSIS IN FLORENCE ACCORDING TO SEX AND AGE

nation was subjected. *This* is the real war tuberculosis, and not the relatively few cases observed in the army, which were to be expected, when one considers that the army included practically the whole of the male population between 18 and 45 years of age, which, broadly speaking, is the time of the greatest mortality from tuberculosis.

All the same, the military tuberculosis gained the attention and the interest of the lay people, and not of them alone, and distracted attention from the ravages of the disease among classes apart from the army.

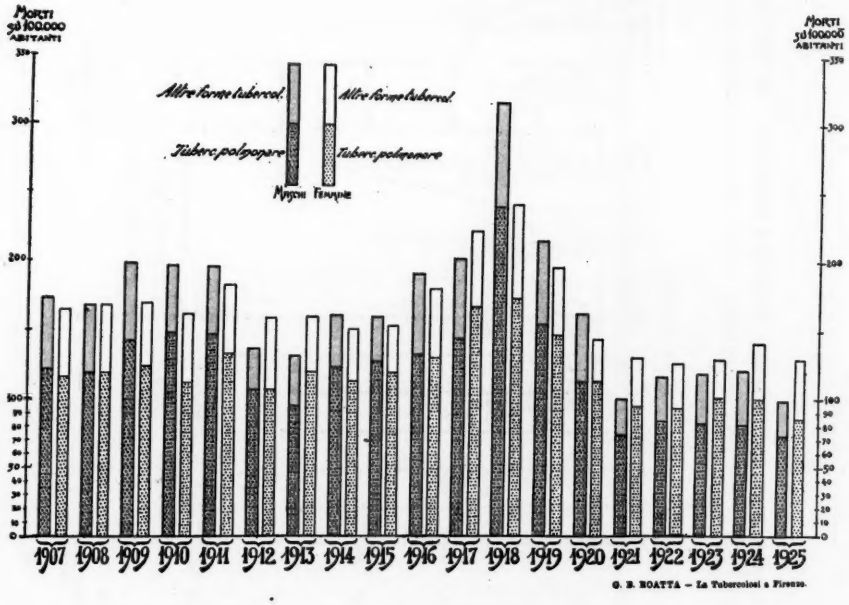

Morti su 100.000 abitanti
Altre forme tubercol.
Tubercol. polmonare
Maschi
Femmine
1907 1908 1909 1910 1911 1912 1913 1914 1915 1916 1917 1918 1919 1920 1921 1922 1923 1924 1925
G. B. ROATTA – La Tubercolosi a Firenze.

PLATE 3

DEATH-RATES FROM PULMONARY AND OTHER TUBERCULOSIS IN FLORENCE, 1907–1925, GROUPED ACCORDING TO SEX

War tuberculosis, in the restricted sense of tuberculosis among the soldiers, was an artificial invention, due to superficial observation and lack of verification.

The age-group (see plate 2) most affected by pulmonary tuberculosis is always that between the ages of 20 and 30, for males as well as for females. The least affected in both sexes is the group between the ages of 5 and 10.

The other forms of tuberculosis reap their harvest among little victims up to 5 years of age. From that time onward the movement is approxi-

mately parallel with that of pulmonary tuberculosis, showing however, a noticeable and decided increase beyond the age of 60.

This fact, based however, on very small figures, would have little value were it not for its persistence in every group period under our consideration.

These data coincide with those observed by other nations, and do not require further comment.

The mortality from tuberculosis in Florence from 1907 to 1920 will be found to be higher among men than women, except in the years 1912, 1913 and 1917, when the female death-rate exceeded that of the male, and in 1908, when it was practically equal (plates 2 and 3).

This mainly relates to the deaths from pulmonary tuberculosis; nevertheless, between the ages of 10 and 15 the female mortality has always been higher, not only in the case of pulmonary tuberculosis but also in other forms.

But in the last five years, 1921–1925, the female mortality from tuberculosis is decidedly higher than the male between the ages of 10 and 40. This female prevalence is especially due to pulmonary tuberculosis.

The above phenomenon is difficult to explain, the more so as there are no available comparative statistics for the other cities of the kingdom. We only know that the same thing has been observed in Milan, where characteristic features of climate and economic conditions are radically different from those of Florence. (Milan is eminently an industrial city, and has a population of over 800,000.)

If this phenomenon were general, and if it were also noted in other nations which, like Italy, have suffered great losses among her male population during the war (over 600,000 for Italy), one might explain the female mortality in postwar years by the fact of the elimination from the population of so many thousands of men. Especially might this be applicable, as the military age (from 20 to 40) coincides with the danger period of tuberculosis.

But in Florence the male mortality predominates for the two years immediately following the war, that is, 1919 and 1920, while the female mortality was noticeably higher in 1912 and 1913 (prewar period) and also in the third year of Italy's participation in the war, that is, in 1917.

All other causes, such as pregnancy, sedentary occupations, contact with tuberculosis cases, either through nursing or in family life, remain the same in all periods, and must therefore be excluded as possible causes.

One might perhaps offer the hypothesis that the diminution in male

tuberculosis is due to better social conditions for the man (the eight-hour day), while in Florence the woman is preëminently a wife and mother, unable to limit the consumption of her energies, so that the improved conditions which affect the men do not influence or ameliorate her way of living.

I put this idea forward not authoritatively but tentatively.

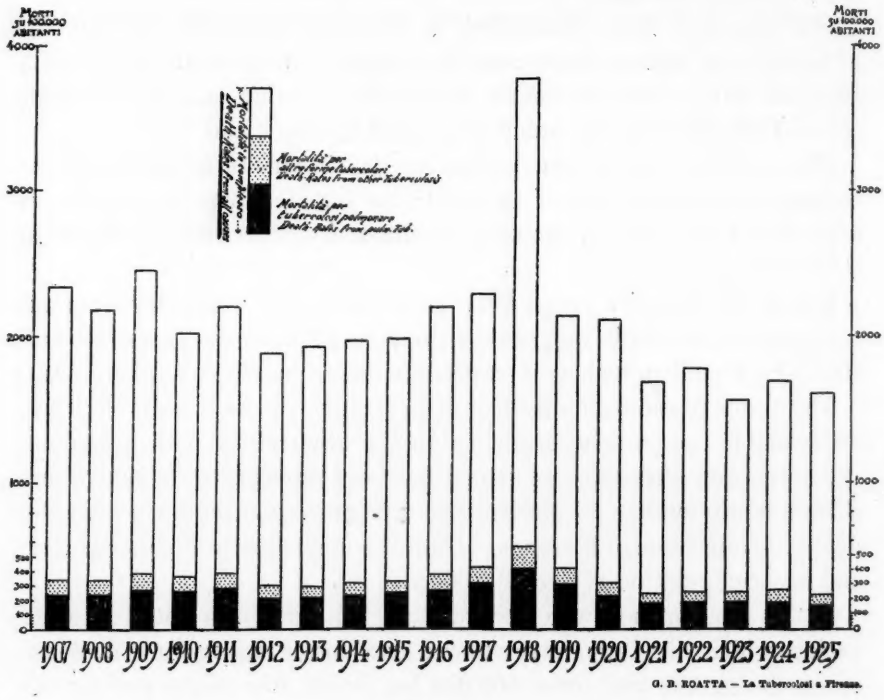


PLATE 4

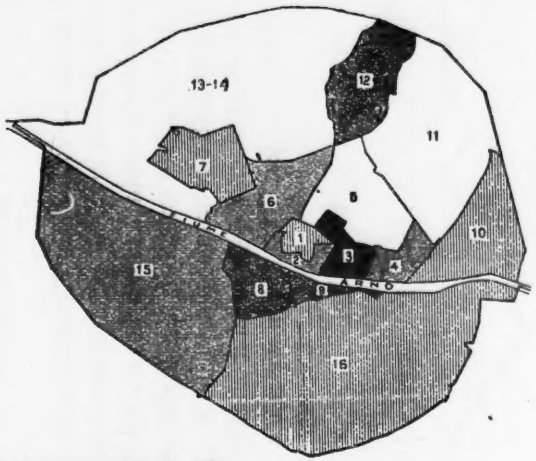
DEATH-RATES FROM ALL CAUSES, PULMONARY AND OTHER TUBERCULOSIS IN FLORENCE, 1907–1925

The mortality from tuberculosis in Florence, for about 20 years from the year 1882 to the end of the century, shows the same general diminution noticeable in other large cities of Europe.

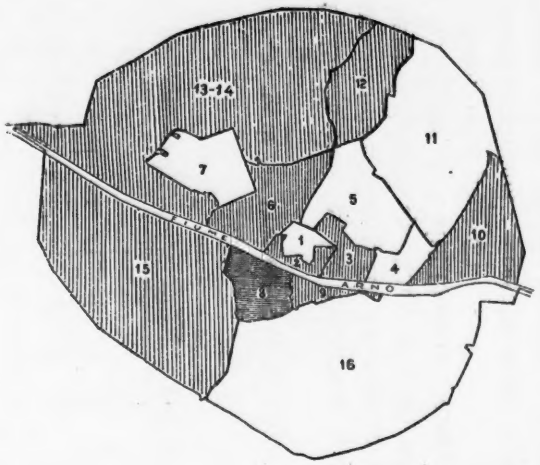
With the beginning of the century there is a tendency to increase. This tendency is shown not only in pulmonary tuberculosis, but also in the other forms, and is not accompanied by an increase in the general mortality. (See plate 4.)

In 1911 the deaths from all forms of tuberculosis were 376, the total

nel quinquennio 1907-1911



nel quinquennio 1921-25



Mortal. per tubercol. polm.
(quota su 100.000 abitanti 1907-1911)

Fino a 150
da 151 a 200
da 201 a 250
da 251 a 300
oltre 300

Zone statistiche

1. Centro
2. Ufizi
3. S. Croce
4. Affrico
5. Viali
6. S. M. Novella
7. S. Jacopino
8. S. Spirito
9. S. Niccolò
10. S. Salvi
11. S. Gervasio
12. Pellegrino-Lapo
13-14 Rifredi-Montughi
15. Pignone-Bellosguardo
16. Ricorboli-Colli
Pian dei Giullari

Mortal. per tubercol. polm.
(quota su 100000 abitanti)

Fino a 150
da 151 a 200
da 201 a 250
da 251 a 300
oltre 300

PLATE 5

DISTRIBUTION OF THE DEATH-RATES FROM PULMONARY TUBERCULOSIS IN 16 STATISTICAL ZONES OF FLORENCE IN THE QUINQUENNIA, 1907–1911 AND 1921–1925

number of deaths being 2,200. We then get a slight diminution up to 1913, when the figures are 290 (general mortality 1,930). In 1914 the ascending line begins again, and reaches its maximum in 1918 with 560 (general mortality 3,770), which is the highest figure recorded.

From this year 1918 onward the figures decrease, and continue to do so until 1921, when we reach 234 (general mortality 1,680): then there is a slight rise up to the year 1924, when we reach 261 (general mortality

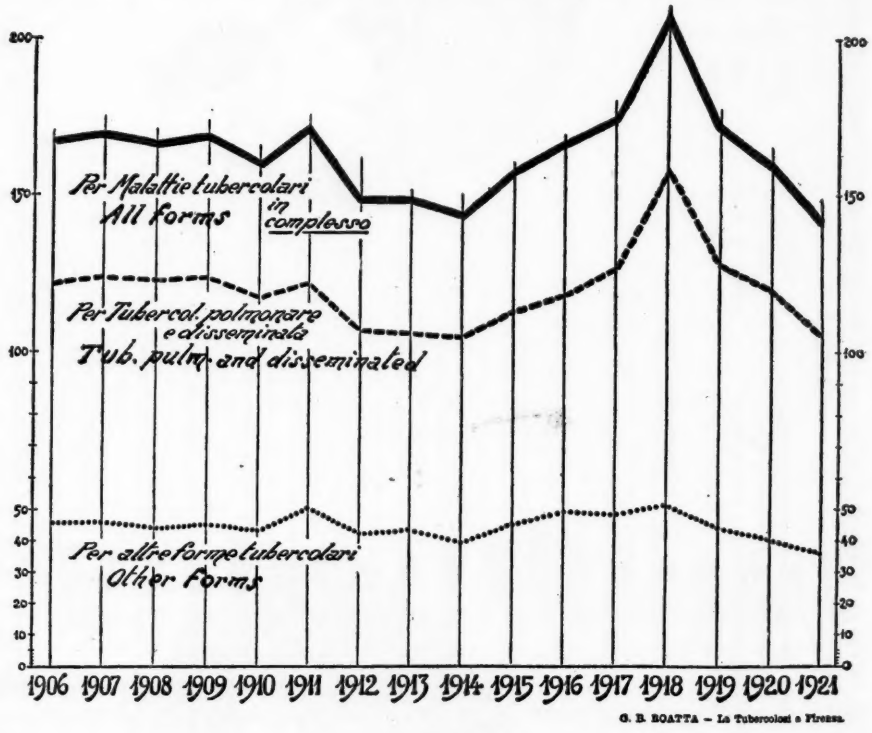


PLATE 6

DEATH-RATES IN THE KINGDOM OF ITALY FROM TUBERCULOSIS, 1906–1921

1,696). In 1925 a considerable diminution is noted, and we have the lowest figure recorded, that is, 228 (general mortality 1,598).

These features, largely speaking, coincide with those of the general mortality in Florence, and with those of the mortality from tuberculosis in the Kingdom. (See plate 6.)

Tuberculosis prophylactic measures being very unequally distributed in the Kingdom, we are, I think, exonerated from seeking an explanation

of this diminution only in the antituberculosis provisions of which I have made mention. Social phenomena are many-sided, and one must guard in their interpretation against the too facile *post hoc ergo propter hoc*. I think that, generally speaking, antituberculosis organization should not be considered (and this in all countries) the only direct cause of the diminution in tuberculosis mortality, but as the index pointing to improved hygienic and economic conditions; and, where we find an efficient and well thought out antituberculosis organization, it is probable that we shall also find a more matured civic apprehension of other forms of social activity.

Let us see therefore what causes may have been the other factors in bringing about this diminution.

Signor Giusti, in the work which I have cited on the mortality from tuberculosis in Florence in the quinquennium 1907–1911, tells us that in studying the distribution of mortality from pulmonary tuberculosis in the various zones, he ascribes great importance to the *density* of the population (inhabitants per hectare). The *density* factor surpasses in importance the other outstanding ones of *overcrowding* (inhabitants per room) and of *social grouping* (percentage of families of the working classes).

STATISTICAL ZONES	DENSITY OF POPULATION PER HECTARE		OVERCROWDING: AVERAGE OF ROOMS TO EACH INDIVIDUAL	
	June 10, 1911	December 1, 1921	June 10, 1911	December 1, 1921
Centro	232	246	1.5	1.5
Uffizi	367	379	1.2	1.2
S. Croce	402	400	1.0	1.1
Affrico	138	144	1.0	1.1
*Viali	116	125	1.5	1.5
S. Maria Novella	182	205	1.3	1.3
S. Iacopino	70	83	1.0	1.1
S. Spirito	294	286	0.9	0.9
S. Niccolò	207	196	1.0	1.1
S. Salvi	32	41	0.8	0.9
S. Gervasio	34	43	1.2	1.1
Pellegrino	38	37	0.8	1.0
Montughi and Rifredi	14	17	0.9	1.1
Ricorboli	14	15	1.0	1.1
Pignone	38	27	0.9	0.9
†Settignano-Rovezzano	8	8	0.8	0.9
†Trespiano-Careggi	3	3	0.8	0.9

* Within the old customs precincts.

† Formerly Fiesole Zones.

In fact, the maximum mortality, not only from pulmonary tuberculosis (exceeding 300), but for general mortality, was found in the zone of S. Croce, which was less overcrowded and less exclusively occupied by the working classes than the zone of S. Spirito, but more *densely* inhabitated. (See plate 5, figure 1.)

On reconstructing the same plan for the quinquennium 1921–1925 a striking change is immediately apparent. The whole chart shows a clearing up. The two group centres of greatest mortality, the one from 251 to 300, and the other over 300, have disappeared, and the zone of S. Croce, which had a mortality exceeding 300 in the quinquennium 1907–1911 from pulmonary tuberculosis, has decreased to under 200.

All the zones show improvement with the exception of two, that is, Rifredi and Montughi (see plate 5, nos. 13 and 14), and this for reasons which I shall presently show. (Table page 661.)

On studying the figures which relate to density and to overcrowding in the several zones, it becomes evident that the slight improvement is of little importance, and absolutely inadequate as an explanation of the diminution of tuberculosis mortality in these localities. Nevertheless, if, instead of merely accepting the global figures for each zone, we take into consideration the figures for each street (figures which I omit for the sake of brevity), we immediately become aware of the fact that the poorest and most densely populated streets show a considerable decrease in their population. On the other hand, the better and more healthy streets have an increased number of inhabitants, the reason being the subdivision of large residences into more numerous flats. This improved distribution of the population is especially noticeable in the district of S. Croce, where statistical variations occur by leaps and bounds, even beyond 100 per cent.

In years past Florence possessed, more than any other city, large palaces and spacious dwellings inhabited by a small number of people. The war and postwar conditions brought about a housing crisis, partly solved by forced measures of division and subdivision of these possibly too spacious abodes.

On the other hand, the increase of mortality from tuberculosis in the districts of Rifredi and Montughi is explained by the fact that what was formerly a country district is now occupied by buildings. In 1911 these zones were largely represented by streets in the making, which are now not only finished but inhabited.

Therefore the *density* phenomenon brought forward by Signor Giusti

for the quinquennium 1907–1911 still continues to play the same important part in the quinquennium 1921–1925.

Other points of view should not be neglected, and first among them comes the important factor of an improved moral sense.

During the six years that I have spent in Florence, always in contact with the poorest classes (for the dispensary which I direct is situated in the zone which up to now has been the most stricken), I have watched the comprehension of the efficacy of antituberculosis prophylaxis and the appreciation of better hygienic conditions gradually develop and steadily increase in the minds of the people.

Tuberculosis is still feared, but no longer with the unreasoning and savage instinct which tends to dissimulation and to the hiding of the disease,—rather with the virile spirit that, fearing danger, faces, fights and conquers it.

This result is entirely due—and this I say, because this I know—to the work of the public-health nurses. To them and to the Committee from whom they depend, I wish to extend my appreciation and to express my admiration.

Another important factor in the diminution of the disease is the better economic condition of the working classes, due to the rise in wages and to the eight-hour day. A proof of this economic betterment is shown by the increased consumption of some important food products, with a relative diminution in others; for instance:

	CONSUMPTION PER CAPITA IN THE YEAR	
	1911	1923
	kg.	*kg.*
Meat (all kinds)	57.1	70.1
Sugar	9.8	14.0
Butter	2.9	3.8
Oil	9.0	12.4
Coffee	3.1	3.7
Beer* (litres)	2.5	3.4
Fish	2.9	2.7
Wine (litres)	180.0	138.0
Alcohol and liquors	2.8	2.0

* Beer is not a national drink, and I think that the larger consumption is due to the tourists who abound in Florence, and not to the working classes.

The larger consumption of meat, sugar, butter and oil is symptomatic, as is also the diminution (unfortunately still too slight) of the consumption of wine and liquors.

These facts are still more symptomatic when one takes into consideration the enormous increase in the cost of living in these last years. Taking the figure 100 as a basis for the food budget of a working-class family for the first half year of 1914, this figure reaches 618 in July, 1926.

PARENCHYMAL PULMONARY TUBERCULOSIS IN CHILDREN[1]

COLE B. GIBSON AND WILLIAM E. CARROLL

It has been pointed out many times that pulmonary tuberculosis occurs in children in three different forms. These are the so called *infantile* type, which is usually widespread and general throughout the lungs; the *juvenile* type, which is confined to the hilum or roots of the lungs; and the *adult* type, in which the disease involves the parenchymal lung tissue, progressing by infiltration, consolidation and cavitation, and retrogressing by means of calcification or fibrosis.

The first, or infantile type, is seen not infrequently in conjunction with generalized tuberculosis involving other organs or structures, and is generally accepted as the most malignant form of the disease. The second, or juvenile variety, is often associated with tuberculous lymph-node enlargements in other parts of the body, is frequently designated as lymphatic tuberculosis, and is probably the most benign form of the affection.

Probably the first, and certainly the second form, occurs with much greater frequency than does the third or adult type. Casual consideration and often close scrutiny have led many writers to assert that this third form, when it occurs in children, proceeds with much the same train of symptoms, complications and terminations as are to be observed in adults who have parenchymal lung lesions. Further, it is the apparent belief of not a few that this form of tuberculosis in children between the ages of five and fourteen years is seen only at rare intervals. Others think that such lesions in this age-group are most benign, heal rapidly, and but seldom tend to chronicity with ultimate fatal issue.

In short, most authorities are to a great extent agreed upon the essential facts and details concerning the infantile and juvenile varieties, but there appears to be some divergence in their views when children with parenchymal lung lesions come under discussion. As a matter of fact, these patients are not discussed to any great extent. One has but

[1] Read at a monthly conference of the Connecticut Tuberculosis Commission with the medical staffs of the Connecticut Sanatoria.

casually to scan almost any medical journal to find frequent references to acute generalized tuberculosis in infants or allusions to masked juvenile or hilum tuberculosis in the pre-adolescent ages, but even close search will only rarely bring to light any pertinent data on tuberculous formations in the pulmonary parenchyma of juvenile subjects. With this in mind it is our purpose to present in this paper certain of our observations upon patients of this type.

It is of course not always possible to make accurate comparisons between the conditions observed in tuberculous children and those in tuberculous adults, because of the diversified nature of the disease, as well as variations in different individuals and the existence of noncomparable states of immunity. We hope, however, by a presentation, in a more or less narrative form, of certain statistical data, to be able to point out certain details that are identical in both, and certain others that are quite dissimilar and noteworthy.

INCIDENCE

By *Incidence* we do not refer to the frequency of tuberculosis in ordinary life, but specifically to our sanatorium inhabitants. All children admitted to Undercliff have necessarily had a diagnosis of tuberculosis made prior to their entrance. Since July, 1920, 855 patients, ranging from fifteen years to five months, have been admitted. The large majority, as stated in a previous communication, were suffering with pulmonary tuberculosis of the so called *juvenile* type. However, 87, or 10 per cent, of them presented signs of tuberculous involvement of the parenchyma of the lungs sufficiently definite to warrant their inclusion in the classification of pulmonary tuberculosis of the accepted adult type.

Of the total number admitted, 54 per cent were males and 46 per cent females, and of those with parenchymal lesions 27 were male and 60 were female. In other words, although 8 per cent more boys than girls were admitted, over twice as many girls were suffering with actual tuberculous involvement of the pulmonary tissue. This accords fairly well with the commonly accepted understanding of incidence as between males and females, although the difference is perhaps somewhat more marked than usual.

The age at the time of admission is relatively nonessential, inasmuch as the important feature here is the age at the time of onset of illness. This, of course, could not always be accurately ascertained; but, by close

questioning and strict search of the past history, we have in the majority of instances arrived at what we believe is a fairly close approximation. The comparison between males and females is shown in table 1.

It is interesting to note that during the same period in the Connecticut State sanatoria for adults parenchymal pulmonary tuberculosis occurred preponderantly in males; that is, 63 per cent of all adult patients were males and 37 per cent were females. These figures are about the reverse of the percentages of males and females in our series of juvenile cases, and clearly show that female children presented themselves at our sanatoria for the treatment of parenchymal tuberculosis far more frequently than did female adults.

TABLE 1

MALE			AGE	FEMALE		
Number	Living	Dead		Number	Living	Dead
1	0	1	1	1	0	1
2	0	2	2	1	0	1
2	0	2	3	2	0	2
0			4	1	1	0
1	0	1	5	2	1	1
0			6	1	1	0
1	0	1	7	0		
2	2	0	8	4	3	1
1	1	0	9	1	0	1
4	3	1	10	6	3	3
4	3	1	11	4	2	2
0			12	13	6	7
4	1	3	13	7	1	6
4	3	1	14	12	5	7
1	0	1	15	5	0	5
27	13	14		60	23	37

HISTORY

Race: A study of the racial stock of the patients in our series was made at the same time that a table was compiled of the racial stock of adult patients who had been admitted to the three sanatoria for adults during the same period. The data are shown in table 2.

It will be observed in table 2 that, while 28 per cent of the adults were of American stock, only 14 per cent of the children were of that lineage, and that, while 14 per cent of the adults were of Italian descent, 28 per cent of the children had Italian ancestors. This might be taken as an

indication that American children are much less prone to develop parenchymal tuberculosis of their lungs than the immediately antecedent generations, and, on the same basis, it might also be taken to mean that children of Italian parentage are far more prone to develop this form of the disease than Italian adults. It would also appear in this light that Irish children are somewhat less liable to this type of involvement than are Irish adults, and so on. On the other hand, it could very easily be argued that such assumptions are based upon a very shaky premise; namely, that the inmates of sanatoria are, in effect, cross-sections of our total tuberculosis population. That this premise is unfounded is probably true, for, after all, only a small part of our tubercu-

TABLE 2

RACE	ADULTS	CHILDREN
	per cent	*per cent*
American	28.0	14.1
Italian	14.0	28.2
Irish	15.0	11.7
Russian	4.3	5.8
Austrian	5.9	7.0
Polish	7.2	5.8
Swedish	3.1	3.5
Canadian	4.1	2.3
Greek	0.9	2.3
English	3.1	4.6
German	4.2	1.1
Czecho-Slovak	1.3	1.1
Danish	0.4	1.1
Jewish	no figures	1.1
Negro	no figures	8.2

lous population reaches sanatoria, and, while the racial groups in these institutions may be a partial index to the racial incidence of the disease, they are probably not accurately representative of the situation as a whole.

Exposure: A history of exposure of a patient to infectious sources is often most difficult to elicit, and is not be to considered of too great importance in the case of adults. The difficulty is often even greater in children, but frequently the history will bring out evidence that is most essential. However, in our 87 cases it was possible to trace a definite exposure to phthisis in only 30 cases.

Previous Illness: During the past seven years a not inconsiderable

number of tuberculous adults has been shown to have been well until attacked by influenza. This disease has also played some part in the history of these children with parenchymal lung lesions, since 18 gave a definite story of having had the affection. The following is a list of the prominent illnesses that had occurred among these children prior to the onset of pulmonary tuberculosis:

	Number of Patients		*Number of Patients*
Measles	43	Varicella	7
Pertussis	23	Parotitis	6
Influenza	18	Scarlet fever	3
Tonsillitis	14	Otitis	2
Pneumonia	9	Nonpulmonary tuberculosis	5

While a history of previous illness was obtained in the cases enumerated, it was not possible to establish in any great number a record of tuberculosis developing as a direct sequence of any antecedent disease. The great majority gave definite information to the effect that considerable time had elapsed between any previous disease and the onset of actual symptoms of tuberculosis, and in these patients the intervals were almost always free from symptoms. So far as histories could be relied upon, the onset was most often insidious and obscure. We were able to definitely link three cases with pneumonia occurring previously. Each of these had a fairly severe pneumonic attack, and tuberculosis followed without an intervening return to health. Two patients gave a history of having developed the symptoms of tuberculosis after tonsillectomy, and one, who had had influenza, did not fully recover from it and the tuberculosis set in as a direct consequence.

Prior to the diagnosis of pulmonary involvement, tuberculosis had certainly been present in other organs of the body in seven cases, not including those of disease of the lymph nodes. We did not include the latter under this definite heading because of the great chances for diagnostic error.

One of these was a girl who had had tuberculosis of dorsal vertebrae five years prior to admission, and this was inactive at the time of admission. After four years in residence the parenchymal pulmonary focus became apparently arrested, and the patient continues well at this time.

A boy of 14 had a tuberculous hip for about seven months prior to admission, at which time he was found also to have pulmonary tuberculosis, to which he succumbed six months later. Another boy of 14 had tuberculosis of the hip seven years prior to admission, and this had be-

come entirely inactive. A year before admission he developed tuberculosis of both ankles and had symptoms referable to a pulmonary condition for about eight months. He likewise did not recover. A boy of 5 was admitted by transfer from Seaside, who at the age of 2 years and 8 months entered a general hospital with a diagnosis of influenza. While there he also had measles and an undefined ocular condition. At the age of 3 years and 6 months he went to Seaside with tuberculosis of the spine and left hip. Six months later definite signs of pulmonary disease were found and he was admitted to Undercliff, where he lived for fourteen months. His inclusion in this present classification is probably erroneous, but is illustrative of the occasionally delayed spread of generalized tuberculosis.

Three other patients had tuberculous peritonitis before admission, when they were found to have pulmonary disease. One girl, who had been ill for a year, made exceptional progress for about eight months, and then the lung disease flared up and she died three months later. Neither of the others recovered. Perhaps before leaving the discussion of previous illnesses we should remark that, though measles and whooping cough occurred more often than any other conditions, their frequency was not made the basis for any conclusions because of their usual high incidence in children.

SYMPTOMATOLOGY

One might conceivably make many diagnoses of tuberculosis of the parenchyma of the lungs by utilizing only physical and X-ray examinations of the patients. But if constitutional symptoms, which are the evidences of toxicity of the process, are thus disregarded one will not only fail to diagnose many cases, but will in the vast majority of instances commit grave errors in prognosis. Symptoms in children are, if possible, of even greater importance than in adults, since they are most often elicited or observed in them with greater freedom and ease than in adults, who consciously or unconsciously either exaggerate or becloud important details of this nature.

Just as in adults, there is in children no one pathognomonic symptom of actual pulmonary tuberculosis and the entire picture of constitutional symptoms is essential in arriving at a proper estimation of the nature, degree and potentialities of the pathological process. The following indicates the frequency of occurrence of symptoms in our 87 cases:

Cough	77	Dyspnea	39
Loss of weight	73	Anorexia	39
Fatigue	65	Night-sweats	26
Expectoration	56	Hemoptysis	23
Fever	54	Hoarseness	11
Pallor	44	Pleurisy	9

It is interesting to note that ten of the children did not cough at the time of admission, when the diagnosis of parenchymal lung involvement was established by means of symptoms, physical signs and X-ray findings. Four had involvement of a single upper lobe, five had disease of both upper lobes, and one had extensive infiltration of all lobes of both lungs. Five of these patients died, one was discharged with a hopeless prognosis, and four became entirely arrested. One among the first five later developed a mild cough, which seemed to be little more than clearing the throat, and by this process raised sputum in which tubercle bacilli were easily demonstrated.

We were somewhat surprised to find that night-sweats occurred in less than one-third of the cases. Most of us have been so much in the habit of enumerating these among the classical symptoms that even the laity give them great importance.

That they do not occur overfrequently has been our experience, but it has been our further observation that, when they do occur, they are, in the majority of instances, of grave prognostic significance. In 26 cases with this symptom 4 had mildly toxic lesions and were eventually discharged as arrested; 7 had extremely toxic processes and were discharged with unfavorable or hopeless prognoses; 2 had extremely toxic lesions, but they improved, and progressed to arrest; and the remainder, 13, had severely toxic lesions and died.

We must conclude therefore that the occurrence of night-sweats in children, whose lungs are definitely invaded by tuberculosis, must be regarded as a definite danger sign.

It was observed that 23 of the children had hemoptysis, or almost as many as suffered from night-sweats. This blood-spitting was seen to occur in all degrees, from streaking of sputum to actual frank pulmonary hemorrhage. It is remarkable, however, that this more or less fearful symptom did not constitute any more severe prognostic menace than did night-sweats, for seven reached arrest, seven were discharged with hopeless or unfavorable prognoses, and less than half, or nine, died. None of these fatalities resulted directly from hemorrhages.

When it is recalled that all the 87 patients were only 15 years old or younger, and that 60 of these were females, it is not surprising that we were able to obtain expectoration in only 55 cases, for it is well known that children expectorate but infrequently unless taught to do so, and that females of all ages are rather inclined to swallow sputum. Likewise, as having some bearing upon this was the fact that 25 of the cases had lesions confined to one lobe or were what might be termed first-stage cases. Kuthy found that sputum was altogether absent in 49 per cent of such patients.

Of the 55 children who expectorated, 40 had tubercle bacilli in their sputum and but 2 of the 40 ever reached an arrested stage of the disease. Eighteen died after discharge, 5 are still in the institution, and 3 are living outside, but with grave prognoses.

To the signs that are to be regarded as of grave prognostic import in children we, therefore, must add the occurrence of tubercle bacilli in the sputum.

Pallor, as a noteworthy sign, occurred in only 44 cases. While this may be considered as remarkable, a still more striking fact was that many of the children with well-defined and extensive active lesions retained so good an appearance as to make one feel that a diagnosis of active tuberculosis was wholly untenable.

As already noted, 10 had no cough and 14 had lost no weight, while several were well beyond standard weight; 21 suffered no fatigue, 31 did not expectorate, 23 had no elevation of temperature, and 48 had no impairment of appetite; yet all of these undoubtedly had active pulmonary tuberculosis at the time of admission, some of them, indeed, presenting on physical and X-ray examination positive indications of extensive disease.

With their appearance of well-being and the lack of symptoms it is remarkable that they had attracted sufficient attention to themselves to make a physical examination necessary and to permit the subsequent diagnosis. It is also worthy of mention that many of these children after admission continued to look and feel so well that it was most difficult to persuade them or their parents of the necessity of continuing treatment.

The ultimately fatal outcome in many of these cases has convinced us that very often a healthy appearance accompanied by liveliness and playfulness may very easily prevent early diagnosis or militate against a proper prognostic estimate of pulmonary tuberculosis in children.

F. H. Hunt (1) in discussing chronic pulmonary tuberculosis in children

has called attention to the paucity of symptoms even in the presence of active widespread disease. Our observations have agreed with his in regard to the infrequency of night-sweats, absence of sputum, and lack of other signs or symptoms of constitutional weakness. Our experience has also coincided with his observation that, unless most carefully watched, these patients are quite prone surreptitiously to play and exercise violently, often with no immediate direful results. It is really amazing how little healthy lung tissue some of them may have, and yet act and appear well and lively. It is perhaps true that this very well-being and excellent appearance sometimes so outweighs the extensive physical signs that it leads to the establishment of a less rigid routine of treatment, and thereby actually shortens the lives of many of these patients.

Lack of symptoms and excellent general appearance even in the presence of widespread parenchymatous involvement have been observed most often in children above two years of age and before the establishment of puberty. This fact might be of even greater interest if considered in light of the statement of Pottenger (2) "that certain symptoms, notably malaise, loss of strength, night-sweats, loss of weight, etc., are due to a disturbance of the normal equilibrium maintained by the nervous and endocrine systems." He specifically mentions the adrenals and thyroid, but it would probably not be wrong to include the gonads in the same category.

Laying aside this speculation, however, we will say briefly regarding the presence or absence of symptoms that, in general, three types of patients have been admitted. The first class had lesions limited to one or both upper lobes; their symptoms were relatively few, evidence of tuberculous toxemia was slight, prognosis was good, and the patient progressed uneventfully to apparent full recovery. Another type had markedly advanced disease, so far as extent of lesion was concerned, but the patients were relatively nontoxic and quite comfortable for a number of years. These, however, eventually broke down completely; most of them died or were taken home with a hopeless prognosis. In the girls the beginning of the terminal phase was often associated with the onset of puberty. The third class was hopelessly ill on admission and survived only from a few days to a few months.

Table 3 shows the distribution of the lesions in the lungs of the children at the time of admission, and likewise indicates the occurrence in the two sexes, with summaries of their present condition.

Lesions confined to one lung occurred more frequently in the right in the proportion of 19 to 11. The outcome seemed slightly more favorable for the right-sided processes, since half of them reached arrest, 4 remained

TABLE 3

		NUMBER OF CASES	NUMBER ALIVE, WELL AND INACTIVE	NUMBER ALIVE, ACTIVE	NUMBER DEAD	NUMBER UNKNOWN
Right upper	M.	7	4	2	1	
	F.	9	5	2	2	
Right upper and middle	M.	1	0	0	1	
	F.	0	0	0	0	
Right upper, middle and lower	M.	0	0	0	0	
	F.	1	0	1	0	
Right lower	M.	0	0	0	0	
	F.	1	0	0	1	
Left upper	M.	3	1	0	2	
	F.	7	3	2	2	
Left upper and lower	M.	0	0	0	0	
	F.	1	0	0	1	
Right and left uppers	M.	8	2	1	5	
	F.	17	4	4	9	
Right upper, middle and left upper	M.	1	0	0	0	1
	F.	1	0	1	0	
Right upper, middle, lower and left upper	M.	3	0	0	2	1
	F.	2	0	1	1	
Right upper, left upper and lower	M.	1	0	0	1	
	F.	6	0	1	5	
All lobes, both lungs	M.	3	0	1	2	
	F.	15	0	1	14	
Total		87	19	17	49	2

active, and 5 died, while of those having left-sided disease only 4 reached arrest, 2 remained active and 5 died.

Lesions confined to one lobe likewise occurred more often on the right

in the ratio of 16 to 10. And it will be noted that again the outcome was slightly better in the former.

From table 3 it will be observed that in practically all of the children, who had more than two lobes involved at the time of admission, the prognosis was hopeless. As a matter of fact, of the 27 cases having disease in two lobes on admission, 16 succumbed. Of the 34 who had evidence of tuberculosis in more than two lobes, 23 are dead and 7 are alive, and the best that can be said of these seven is that one is considered to have a doubtful prognosis, the other six being hopeless.

In our experience these figures are not matched by the ultimate behavior of adults with lesions of similar extent. Our statistics lead us to aver that minimal or moderately advanced anatomical distribution of tuberculosis in children is of much graver import than the same amount of disease in adults.

The average duration of illness in those patients who died was as follows:

Right upper lobe	1 year, 7 months
Left upper lobe	3 years, 7 months
Both upper lobes	1 year, 11 months
Right upper, both left	1 year, 9 months
Right, all lobes, and left upper	1 year, 6 months
All lobes, both lungs	1 year, 3 months

The composite average duration of illness in all patients who died was one year, eleven months.

Nineteen of the cases in the series recovered from their tuberculosis by reaching a stage of arrest, and their lesions remain inactive at this time. Nine of these had disease confined to the upper lobe of the right lung, 4 to the upper lobe of the left lung, and 6 had involvement of both upper lobes.

The average length of illness of those children having the disease confined to the right upper lobe was four years and five months; left upper lobe, four years and two months; and both upper lobes, three years and five months. It seems rather extraordinary that the average duration of activity in both upper lobes was shorter than that of either single upper lobe. The composite average duration of illness in all patients who reached arrest was four years.

With one exception all of these patients made constant and progressive improvement. The single exception was a girl who had frequently recurring attacks of follicular tonsillitis. For two and a half years this girl

failed to show improvement in her general condition in spite of the fact that there was no increase in the extent of her pulmonary lesion. Finally the tonsils were removed, after which the patient gained rapidly. None of the patients suffered from any complication of tuberculous origin except three who had slight hemoptyses while under treatment. There was no pleurisy, either serous or plastic, no laryngitis, enteritis or ischiorectal abscess, and no eye conditions, such as corneal ulcers or phylctenular conjunctivitis. However, intercurrent disease was not uncommon. Five patients suffered severe attacks of epidemic influenza, apparently without ill result. One was operated upon for acute appendicitis, while another had tonsillectomy performed for recurring tonsillitis; both made rapid and uneventful recoveries. One patient had herpes zoster and one acute otitis media. In no instance, except in the case of the girl with recurring tonsillitis, did these intercurrent illnesses interfere with the progressive healing of the pulmonary lesion.

In general, the course of the disease was steady and uninterrupted improvement. Symptoms once abated did not recur, except for the slight hemoptyses mentioned above. Physical examination and X-ray findings showed steady progress toward fibrosis and calcification. In no patient was there extension of the lesion beyond the area present on admission. In only one instance did râles reappear after they had been found absent. Two of the patients had positive sputum on admission. The bacilli disappeared within a few months and could never again be demonstrated.

The majority of the cases reaching arrest showed, by means of roentgenograms, definite indications of a fibrosing process, or calcification of localized areas, or both. One case, however, proved a very striking exception and demonstrated the truth of Gardner's hypothesis (3) and the accuracy of Krause's assertion (4) that "specific tuberculous changes, of a proliferative character, can resolve, heal and disappear." This patient was a boy of 11 years, admitted with cough, expectoration, loss of weight, fatigue, and night-sweats. Physical examination, confirmed by X-ray, revealed tuberculous infiltration of the upper lobes of both lungs. Tubercle bacilli were demonstrated in his sputum, and shortly after admission he had had an hemoptysis of several tablespoonfuls in quantity.

He received general heliotherapy and the other sanatorium routine steadily for three years and eight months, and was then discharged as arrested. No adventitious signs could be elicited at his final examina-

tion, and roentgenograms revealed no evidences of the disease that had surely been present four years before.

It will have been noticed in table 3 that 49 of the patients have died either at the sanatorium or after discharge. While, of course, the majority of the patients in our series were females, yet the fact that 33 of these deaths were among that sex rather forcibly emphasizes the generally accepted ratio of mortality between the sexes. A study of the ages at death likewise substantiates the oft-repeated assertion that the establishment of puberty in tuberculous girls is frequently followed by rapid extension of disease, and death.

Female		*Male*	
Age at death	*Number*	*Age at death*	*Number*
5 years or below	2	5 years or below	3
6 years or below	1	6 years or below	2
10 years or below	1	8 years or below	1
11 years or below	2	9 years or below	1
12 years or below	3	11 years or below	2
13 years or below	4	14 years or below	2
14 years or below	6	15 years or below	2
15 years or below	8	17 years or below	1
16 years or below	3		
17 years or below	3		
18 years or below	2		
	35		14

In New England most girls probably reach puberty during the thirteenth, fourteenth or fifteenth year, and it was in these age-groups that the peak of mortality in girls was reached, the fifteenth year having the highest rate. After the fifteenth year there appeared to be a decline, probably due to the fact that puberty had already been reached before the disease became established.

We have already in a previous communication discussed the establishment of puberty and its effects upon our female patients. Our most recent figures more definitely emphasize the gravity of prognosis for those females with active tuberculosis who reach that critical age. From a study of the length of illness of those patients who died, it has also been impressed upon us that the establishment of puberty is followed most frequently by pronounced exacerbations of the disease, and the expectancy of life, as compared with other age-groups with active tuberculosis, except only the infantile group, is greatly diminished.

COMPLICATIONS

A list of the complications that occurred in our series of cases reveals the fact that fortunately the majority of the patients did not suffer from superimposed afflictions. Moreover, by far the greater part of the complications observed were a part of the tuberculous process, or were the ascendant symptoms of tuberculosis occurring in other parts of the body at the same time as the parenchymal lung involvement. These were as follows:

Pleurisy	10	Empyema	2
Otitis	10	Ischiorectal abscess	2
Spontaneous pneumothorax	7	Pyopneumothorax	1
Laryngitis	7	Enteritis	1
Peritonitis	1	Bronchiectasis	1
Diarrhea	3	Epilepsy	1
Appendicitis	3	Endocarditis	1
Hydropneumothorax	2		

Among the 10 cases having pleurisy 5 had effusions.

It is not possible to say what percentage of the otitis cases was positively tuberculous, but probably the majority were.

We were somewhat surprised to note that slightly over 8 per cent of our cases developed spontaneous pneumothorax. This is certainly higher than we would casually have thought, and, in fact, it is higher than the figures many authorities give when discussing the accident among adult patients. Six of our patients were females and one male. The tear was in the right pleura in four of these and in the left in three. Five of the 7 died within a few days, and among these were two sisters. One girl developed hydropneumothorax, resorbed most of the fluid, progressed well for a year, abandoned treatment, and another year later died. One girl remains alive at this time seven months after the development of the condition.

Tuberculous laryngitis occurred in 6 girls and one boy. All eventually succumbed to the disease, but one girl made an excellent recovery from the laryngitis during an interval of quiescence.

The most remarkable thing about the complications observed in our series was their scarcity. It has been our experience with adult patients in the majority of cases, that when a certain stage of saturation is reached the disease overflows from the lungs and involves other organs or structures, frequently as definite tuberculous disease, such as enteritis, peritonitis, or meningitis, or gives rise to certain reciprocal abnormal

conditions of the kidneys or heart. Such occurrences were not noticeable to any appreciable degree in our series, and it appeared that the toxicity of the pulmonary lesions alone, in the majority of the cases that did not recover, was responsible for death. These results might be considered to have some bearing upon the slighter power of immunity in children of our age-group as compared with adults. It is interesting to recall also that when one of these children did develop a tuberculous complication the outlook for recovery was exceedingly poor.

SUMMARY

1. Slightly over 10 per cent of 855 children under 15, admitted to Undercliff, showed definite tuberculous disease of the parenchymal lung tissue.

2. More than twice as many girls as boys were so diseased.

3. Children of American, Italian, Irish and Negro parentage comprised over 50 per cent of these admissions.

4. A definite history of exposure to an open case of tuberculosis was obtained in less than half of the cases.

5. Measles, pertussis, influenza and tonsillitis were the most frequent previous illnesses.

6. Cough, loss of weight, fatigue, expectoration, and fever were the most prominent symptoms. Night-sweats occurred with less frequency than in adults, but proved to be of grave prognostic omen. Hemoptysis occurred about as frequently as night-sweats, but was not of the grave import that it usually is in adults.

7. An excellent general appearance and lack of symptoms did not preclude the possibility of widespread tuberculosis of the lungs.

8. The most frequent location of the disease was in both upper lobes. When confined to one lung the lesion was most often right-sided.

9. Involvement of more than two lobes at time of admission always denoted a poor prognosis.

10. Forty-nine of the patients died, 17 are alive with active disease, and 19 reached arrest and continue well.

11. Fifty-eight per cent of the females admitted died. Fifty-one per cent of the males did not recover. Of the total deaths 71 per cent were among the female patients, and 29 were males.

12. The establishment of puberty in the females was accompanied by increased gravity of the prognosis.

13. Complications were few but of ill omen.

14. The presence of tubercle bacilli in the sputum of children almost always renders the chance for recovery hopeless.

In conclusion we believe that we may state:

First: Tuberculous parenchymal lesions occur in about 10 per cent of those children who are diagnosed as tuberculous, and since such patients often present real problems in treatment they should be sought out assiduously and placed on a most rigid routine regardless of apparent lack of signs of toxicity.

Second: The mortality of children under 15 years of age suffering with parenchymal tuberculosis is higher than that of adults. Except for the infantile group, girls at the age of puberty with parenchymal involvement give the highest of all death-rates from pulmonary tuberculosis.

Third: As already recounted and pointed out in the summary, the behavior of children with definite lung tuberculosis differs somewhat from that of adults similarly affected. Principally, they are prone to have fewer symptoms and complications than adults, but the death-rate in children is higher. Certain symptoms in children seem also to be of much greater importance in making an accurate estimation of the disease than are the same manifestations in adults.

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ALTERATIONS IN THE PERMEABILITY OF SKIN CAPILLARIES DURING THE COURSE OF TUBERCULOSIS[1]

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There seems little doubt that a seasonal variation of morbidity and mortality occurs in tuberculosis. The mortality curve shows a distinct spring and fall peak, and statistics concerning the onset of activity indicate a far greater preponderance of spring cases. In recent years a number of investigators have been interested in this phenomenon.

Hamburger (1) associated the spring increase in disease activity with an increase in allergic phenomena during this season. Peyrer (2) found the skin much more susceptible to tuberculin from December to July, and in the same group of children obtained more positive reactions during this period. He found that actual morbidity of the ectoderm from tuberculous processes reached its maximum in March and April. Rusnyak (3), in an analysis of mortailty and morbidity in the Viennese population, analyzes the spring and fall rise in tuberculosis mortality. Practically all nervous diseases have a similar curve. Rusnyak calls attention to the fact that the blood calcium is low in the winter months (tissue calcium high). Pellagra, with its admixture of ectodermic and entodermic manifestations, follows morbidity and mortality curves quite similar to those of tuberculosis (Jobling and Petersen (4)).

Hartwich (5) has also studied the relation of season to tuberculous activity, and Huebschmann (6) in his analysis of the origin of miliary tuberculosis regards this seasonal influence as evidence that a purely mechanical concept cannot be maintained, and believes that we must seek some change in the receptive condition of the endothelium at different times of the year to account for the fluctuations in morbidity and mortality.

Hagen (7) definitely associates changes in the capillaries with the change in resistance. On direct capillary microscopy he determined (1)

[1] From the Department of Pathology, University of Illinois College of Medicine, and the Research Laboratory of the Chicago Municipal Tuberculosis Sanitarium. Read at the twenty-second annual meeting of the National Tuberculosis Association, Washington, D. C., October 6, 1926.

daily variation in the capillaries, the skin capillaries becoming wider in the afternoon and evening as compared with the morning, (2) *monthly* variations in the capillaries of women, associated with the menstrual cycle, and (3) finally *seasonal* variations, the skin capillaries being relatively spastic in the winter and dilated in the spring. It is probable that these observations on the skin are largely applicable to the capillary bed of the lung.

Dilatation of the capillary (stimulation of the endothelial cell) goes hand in hand with increase in the capillary permeability; this with increase in local tissue activity; this with a slight shifting of the hydrogen-ion concentration, with lessened calcium and increased potassium in the tissues. Pharmacologically, we group it as a parasympathetic state. The opposite condition, the sympathetic status, is that in which the capillaries are less permeable, the arterioles contracted, and the tissues containing more calcium and less potassium, with relative increase in alkalinity and lessened tissue activity.

Into this balance enter at least three major controlling mechanisms and perhaps many minor ones, the nature of which is still obscure. These three include the control of the *autonomic nervous apparatus*, probably largely local in the origin and distribution of impulses but nevertheless under central influence. The effect of the impulse conveyed to the cell (endothelial, smooth musculature, glandular, undifferentiated connective tissue) is conditioned by the preëxisting status of the cell (whether active, at rest, fatigued, etc.), so that the actual response may, under certain conditions, be reversed or paradoxical. The control by *biochemical and bioelectrical alterations*, inseparably connected with the nervous control because the nerve impulse uses ionic rearrangements as the mechanism by means of which its effects are mediated, and finally the control by means of the *endocrine secretions*. We have discussed these factors in a series of papers, and shall therefore not enter into the details at this time. In previous papers we have called attention to certain alterations in capillary permeability, as studied in dogs, and the theoretical relation to the tuberculous process (8).

THE CLINICAL EFFECT OF INCREASE IN CAPILLARY PERMEABILITY

What clinical effect does increase in capillary permeability and its associated biological alterations have on a tuberculous process?

We have pointed out the seasonal association in our introduction. That the menstrual alteration is associated with a deleterious effect is

probably an established clinical phenomenon. Indeed, the premenstrual rise in temperature is of significance even in diagnosis (Kraus (9), Goodwin (10), Bezançon (11)).

Menstruation: In the premenstrual period the capillaries become more permeable (Petersen and Milles (12)), and the alteration reaches its maximum with the onset of menstruation and subsides rapidly to normal. We have been particularly interested in the phenomenon, for we have before us a clear-cut biological alteration, with an associated lowering of resistance to tuberculous infection, in which we can seek some of the factors that deal with resistance (13).

Moltner, as well as Gelmi (14), have found that castration in guinea pigs is followed by increased resistance to tuberculous infection. Bricker (15) has noted the same factor for rabbits, and Bauer (16) has called attention to related clinical observations. These include the mild course of tuberculosis in hypogenalitism as contrasted with the devastating progress of tuberculosis that begins with puberty.

But in menstruation we do not deal with a disturbance of the vegetative balance that is wholly one-sided (parasympathetic), but more likely with fluctuations in the balance, with alternating periods of increase and reduction. This is the usual course of events when endocrine agents are slowly absorbed (Petersen (18)), and seems to be the clinical conclusion of some (Guillaume and Godel (19)). Couland (21) has observed the diasppearance of the tuberculin reaction before and during menstruation.

Scherer (quoted by Hagen (17)) showed that, the earlier the menstruation, the greater the probability for tuberculosis and the worse the prognosis. Increased râles and a tendency to hemorrhage are found in the premenstrual and menstrual period (see also *Statistical Bulletin, Metropolitan Life Insurance Co.*, December, 1920, ii, 3). Following the menstrual cycle the patient may show decided improvement (Bergeshausen (20)).

Pregnancy: It is not expedient to review the voluminous literature dealing with pregnancy and tuberculosis. Certainly parturition is harmful. Repeated pregnancies are without doubt injurious. Certain, too, seems the fact that the biological alterations that we find in pregnancy are frequently associated with focal activation of other diseases, both infectious and noninfectious in origin.

Of the various *psychic* derangements, dementia precox stands out with

its high tuberculosis mortality. Whether this is to be associated with the probable endocrine change suspected cannot be definitely stated. Thus the rôle of the thyroid is by no means clear.[2] Alcoholism, formerly accepted as distinctly injurious, is, as a result of more recent studies, now at least debatable.[3] On the other hand, the importance of nutrition, and more especially certain vitamines, in maintaining resistance is moving more and more into the foreground as a result of the experience of the past ten years.

THE CLINICAL EFFECT OF DIMINISHED CAPILLARY PERMEABILITY

By general consent several conditions have been recognized with which an increase in resistance to tuberculosis seems associated. These include senility and nephritis (arteriosclerotic), asthma and emphysema. Of these the two latter presumably exert their effect on the local pathological process by means of changes in vascularization, and are to be placed in the same category as mitral stenosis.

Nephritis: Nephritis is of particular interest to us for the purposes of this analysis because in nephritis we deal primarily with a disease of the capillaries and of the autonomic tonus of the arterioles. In acute glomerular nephritis (*the capillaropathia acuta universalis* of Kylin (25)) we have a condition in which the capillaries of the body are injured, with an increase in permeability as one of the expressions of this injury. Tuberculosis, when found in association with this form of injury, is usually of

[2] Thyroses of mild degree are common associates of tuberculosis, particularly in the early stages of activity; active tuberculosis incident to a preëxisting disease seems to be uncommon (Mayo Clinic; see paper of Webb). Coulaud (21), on the other hand, believes that thyroid activity lessens resistance to a tuberculous infection. In a small series of goitre patients we have found that some have quite permeable skin capillaries, while others are within the normal range, especially those with increased blood-pressure.

[3] In the older statistics the rôle of alcohol is emphasized as one of the factors that leads to lowered resistance toward a tuberculous infection. In the more recent studies this relationship is by no means clear-cut. Both Arnould (22) and Samson (23) have reached the conclusion that chronic alcoholism may indeed cause an increase in resistance, and Orth (24), in postmortem examination of many acute and chronic alcoholics, found no evidence that alcoholism, carried to a terminal delirium tremens, was associated with progressive tuberculous lesions. Alcoholism associated with the consumption of malt liquors offers a problem that differs essentially from that produced by strong drinks. While it is probable that alcohol, by direct action on the cell-membrane, renders it more permeable for a short period of time, a reversal evidently sets in very rapidly, with a relatively prolonged period of impermeability. Alcohol would under such conditions have many of the effects of a mild tuberculinization.

a progressive character. With hypertonia, on the other hand (with benign or malignant sclerosis of the kidney), a coexisting tuberculosis is practically always benign in character, as it frequently is in gout as well.

In hypertension, as will be shown later, we deal with relative impermeability of the capillaries, while in acute nephritis the capillaries are permeable but the arteriole may be spastic.

Senile Tuberculosis: With advancing age the relative sympathetic tonus of the body is increased, the tissues contain more calcium and less water, and permeability is diminished. With tuberculous infection there is a well-recognized tendency toward proliferation, with suppression of irritative infiltration and exudation and with a clinical picture that is essentially benign.

Peripheral-Visceral Interrelation: We have one other clinical correlation which we should like to mention in passing, namely, the fact that peripheral tuberculosis is frequently associated with clinically benign internal lesions. A similar relation has been found in experimental animals. In a guinea pig with cutaneous inoculation and later generalization, the surgical removal of the local lesion is followed by a more rapid progression of the internal lesions. In an individual with autopsy inoculation of the skin of the hands (the tubercles persisting for years) Jaffé observed the sudden disappearance of the cutaneous lesions preceding the rapid development of a generalized tuberculosis that terminated the life of the individual in a few months (26). We have discussed the antagonistic orientation of the autonomic status of the visceral as contrasted to the peripheral region of the body in a previous paper (27).

THE CAPILLARY PERMEABILITY OF THE SKIN IN THE NORMAL PERSON, IN MENSTRUATION, IN PREGNANCY AND IN VARIOUS CLINICAL CONDITIONS

In view of the probable relation of capillary permeability to the relative activity or quiescence of the tuberculous focus, we endeavored to obtain information concerning the permeability of the capillaries in various conditions and have made use of the blister method, described in a previous paper (28).

The method itself is relatively simple. A small cantharides plaster is applied at a definite time (usually 4 A. M.) for a definite period (6 hours) to the skin of the inner surface of the arm just below the elbow.

After removal, the exact time when the first blister appears is noted (*blister time*). When sufficient fluid has collected, it is at once drawn and at the same time a blood sample collected from the ear-lobe. The protein content of the blister fluid and the protein of the blood-serum are now determined by means of the refractometer and the *Index*, $\frac{\textit{protein in blister}}{\textit{protein in serum}}$, is determined. It is obvious that, the larger the figure, the greater the relative permeability. The reactivity of the patient, that is, the *Inflammatory Index*, is expressed by the *Ratio* $\frac{\textit{permeability ratio}}{\textit{blister time (in hours)}}$. This figure will be large when the patient responds in a short time and small when it requires a long time for the blister to form. Inasmuch as we have entered into a discussion of the method elsewhere in detail, we have here merely outlined the method.

Normals: In a study of some 66 normal men we have determined that the average *Permeability Ratio* for the group was 68 and the *Inflammatory Index* 10.5. The individuals varied from a low of 57 to a high of 84. The men were examined for tuberculosis (history, physical examination and roentgen picture, the latter through the kindness of Dr. A. Hartung,) and it will be observed that those that had had more than the normal amount of infection predominated in the *Impermeable Group* and in the group with *Low Inflammatory Index* (table 1).

Menstruation: Together with Milles we have examined the relation to menstruation (29) and here a distinct change in permeability has been noted. While the intermenstrual ration is 72, preceding menstruation this increases to 75, and on the first day of menstruation reaches 77. There is evidently a striking change in the blister time as well, which in the intermenstrual period was 5.8 hours and dinimished to 3.6 hours before menstruation. The *Inflammatory Ratio* for the intermenstrual period was 12.4, for the premenstrual period 20.8, and for the first day of menstruation 14.

Pregnancy: In the puerperium there is likewise an increase in permeability. Particularly the pathological cases are found to have a marked tendency to group at the permeable end of the scale. Our averages were 70.5 for the antepartum cases and 73.6 for the postpartum cases (100 cases examined (30)).

TABLE 1

Relation of Inflammatory Index of normal students to tuberculous infection

LOW GROUP					HIGH GROUP				
Student number	Inflammatory Index	History of clinical tuberculosis	History of family tuberculosis	Roentgen diagnosis of tuberculosis*	Student number	Inflammatory Index	History of clinical tuberculosis	History of family tuberculosis	Roentgen diagnosis of tuberculosis
6	3.5				35	10.4			
5	5.2		+		63	10.5			
22	5.8				38	10.5			
44	6.4	+		+	16	10.5			
27	6.5	+	+		21	10.6			
10	6.7		+	+	7	10.7			
30	6.7	+	+	+	25	10.8			
50	6.9				37	11.3			+
19	7.0			+	60	11.4			
1	7.1				42	11.6			+
12	7.1				28	12.0			
32	7.3		+	+	46	12.0			
9	7.4				48	12.0			
20	7.4				66	12.0			
3	7.6				49	12.1			
41	7.7				53	12.3			
8	7.9	+	+	+	56	12.3			
4	8.1				23	13.0			+
26	8.1				61	13.0			
31	8.3				51	13.2			
36	8.5				33	13.4			
24	8.6				15	14.0			
13	8.7		+	+	58	15.0			
17	9.0		+	+	59	15.0		+	+
18	9.0	+		+	52	15.0			
29	9.3				11	15.2			
43	9.4				14	15.5			
2	9.5		+	+	62	17.0			
34	9.6			+	40	17.5			
39	10.0	+		+	64	17.7			
45	10.1			+	65	18.2			
47	10.3				54	18.5			
57	10.4			+	55	18.5			

* In this group Dr. Hartung has included only such students as show more than the normal hilum shadow, with distinct evidence of parenchymal alteration.

Tuberculosis: In a previous paper dealing with observations on several hundred patients ill with various diseases, we observed that in the tuberculous group the exudative and progressive cases had a higher permeability than patients of the chronic type. In the latter group, too,

TABLE 2

1A and B cases (females)

NUMBER	RACE	AGE	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX
								hours				
163	W.	21		98	82	158	−	9	7.73	4.57	0.59	6.5
162	W.	40	Improved	98	80	175	+	7½	8.57	5.49	0.64	8.5
165	W.	35	Stationary	98.2	84	192	−	9	8.49	5.60	0.66	7.3
164	W.	19		97.6	84	134	−	6	7.10	5.09	0.71	11.8
160	W.	21	Improved	98	72	152	−	6	8.20	6.20	0.75	12.5
161	W.	21		98.6	88	108	−	7	7.41	5.90	0.79	11.2
166	W.	16	Active; not doing well	99.6	90	128	−	7	7.85	6.10	0.77	11.0
167	W.	24		98.6	74	140	−	8½	8.16	5.33	0.65	7.6
168	W.	33	Fibroid, plcurisy	98.8	100	112	+	8	8.16	5.49	0.67	8.3
Averages.....		25				144		7.5			0.69	9.4

Total cases, 9.

TABLE 3

1A cases (females)

NUMBER	RACE	AGE	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	BLOOD PRESSURE	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	
									hours					
89	W.	20	Chronic rheumatism	97.8	60	127	−		8	8.28	5.20	0.62	7.7	X-ray: hilum shadow increased
83	C.	20		98.6	68	119	−		6	8.92	5.69	0.63	10.5	
68	W.	15	Adenitis	98.6	120	116	−		4½	8.36	5.39	0.64	14.0	
69	W.	14	Adenitis; bilateral apical tuberculosis	98.6	96	102	−		4	8.08	5.29	0.65	16.0	
84	W.	17	Arrested	98.4	88	138	−		11	8.65	5.69	0.65	5.9	
82	W.	20		98.4	82	138	−		7½	7.95	5.20	0.65	9.3	
75	W.	26		98	84	126	+		6	7.86	5.29	0.67	11.6	X-ray: moderate infiltration right upper
80	W.	20		98.4	90	126	−		6	8.06	5.49	0.68	11.3	
87	W.	20	Adenitis	98.4	88	121	−		6	8.06	5.49	0.68	11.3	X-ray: hilum and parenchymal involvement
74	W.	26	Not menstruating	98	78	133	−		6	8.70	6.11	0.70	11.6	
81	W.	28		98	88	140	−		6	7.81	6.30	0.72	12.0	X-ray: far advanced tuberculosis, displacement of heart and mediastinal contents
79	W.	21	Tuberculous adenitis	98	54	157	−		6	7.85	5.80	0.73	12.1	
88	W.	8	Bronchitis	97.6	88	51	−		9	6.98	5.09	0.73	8.1	Pirquet positive
91	W.	35		99.2	96	100	−		12	7.73	5.70	0.73	6.0	
76	W.	40	Tuberculosis	98	90	108	−		6	7.95	5.70	0.74	12.3	
90	W.	24		98.4	100	120	−	132/78	6	7.73	5.78	0.74	12.3	
77	W.	26		98.4	80	135	−		6	7.73	6.10	0.78	13.0	
78	W.	20	Menstruating*	98.6	88	116	−		6	7.85	6.30	0.80	13.1	
151	W.	18	Improving*	98.6	80	135	−		6	7.95	6.50	0.82	13.6	
Averages.....		22				121			6.7			0.69	10.8	

Total cases, 19.

* Menstrual or premenstrual not included in averages.

TABLE 4

MAA cases (males)

NUMBER	RACE	AGE	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	BLOOD PRESSURE	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	
									hours					
182	W.	29		97.6	70	180	−		6½	8.28	4.60	0.55	8.4	
186	W.	38	Improved	98	72	168	−	100/60	11	7.84	4.76	0.60	5.4	
176	C.	59	Mitral regurgitation	96.8	78	153	+	150/90	6	9.13	5.69	0.62	10.3	Wassermann, ++
178	W.	28	Fibroid	97.4	78	130	+	120/80	10	7.20	4.57	0.63	6.3	
181	W.	32	Improved; fibroid	97.8	82	158	+	130/76	6½	7.95	5.09	0.64	9.8	
61	W.	23	Improving	98.4	80	163	−		4	8.35	5.39	0.64	16.0	
171	W.	35		96.8	76	212	−		10	8.60	5.49	0.64	6.4	
188	W.	66	Improved	98	70	133	+		6	8.06	5.20	0.65	10.6	
62	W.	26		98.6	74	137	−		9	8.28	5.60	0.67	7.4	
170	W.	29	Fibroid	98.2	74	149	+		6	8.92	6.00	0.67	11.1	
177	W.	19	Improving	98	80	152	−		6	8.49	5.69	0.67	11.1	
184	W.	41	Inactive	98.6	76	146	+		6½	7.06	4.78	0.67	10.3	
190	W.	46	Fibroid	97.4	82	163	−		6	8.06	5.40	0.67	11.1	
194	W.	23	Fibroid	97.8	80	180	+	108/65	6	8.92	6.00	0.67	11.6	
179	W.	51	Fibroid	97.6	78	183	−	140/90	6	7.95	5.49	0.69	11.5	
183	C.	31	Stationary	98.6	68	178	+	104/70	6	8.38	5.80	0.69	11.5	
169	Y.	33	Active	97.8	92	106	+	100/70	12	7.63	5.40	0.70	5.8	
173	W.	21		97.8	72	166	−	140/90	6	8.38	5.90	0.70	11.6	Wassermann, +
180	W.	23	Stationary	98.6	76	141	+		8½	8.92	6.30	0.70	8.2	
189	W.	21	Active	98.2	80	170	−		8	8.70	6.10	0.70	8.7	Wassermann, A. C.
195	W.	42	Stationary	98.4	78	166	+*		8	7.20	5.09	0.70	8.7	
65	W.	33	Fibroid	98.6	74	162	+	130/70	6	8.80	5.86	0.71	11.0	
191	W.	49	Fibroid	98	88	120	−	110/80	6	7.4	5.40	0.72	12.0	
66	W.	46	Cavitation	99	110	99	+	120/80	9	6.44	4.76	0.73	8.1	
185	C.	40	Active	92.2	86	157	+	100/60	10	8.14	5.98	0.73	7.3	
67	C.	26	Fibroid	98.2	80	136	+	100/65	6	8.49	6.30	0.74	12.3	
172	W.	26	Active	98.2	78	120	+		6	8.50	6.30	0.74	12.3	
174	W.	28		97.8	72	135	+		6	8.70	6.50	0.74	12.3	
175	W.	19		97.6	80	131	+	110/80	8½	8.28	6.10	0.74	8.7	
192	W.	41		98.6	84	134	+		9	8.81	6.60	0.75	8.3	
187	W.	17		97.2	84	102	+*		6	8.28	6.50	0.78	13.0	
193	W.	23		98.2	76	132	+		6	7.99	6.30	0.79	13.1	
71	W.	26		98.6	84	128	−		6	8.81	7.10	0.80	13.3	
Averages.....		33				148			7.1			0.68	10.1	

Total cases, 33.

* Antiformin.

the blister time was prolonged, so that the patients had a low Inflammatory Index.

The material here reported deals with approximately 250 patients studied at the Chicago Municipal Tuberculosis Sanitarium. Of these we have grouped the first 200 cases according to the clinical condition of the patient, as determined by the examination of the attending staff-physicians (N. T. A. classification). We are of course aware that this may not give us an actual index of clinical activity, but it at least affords an unbiased method of classification for our purpose.

The last 50 cases studied have been males and we have grouped them according to the probable duration of the activity. This tabulation is ovbiously subject to a large factor of personal interpretation, in addition to the fact that the more chronic cases will appear in the older age-group in which we may normally anticipate some reduction of permeability.

In tables 2 to 12 the details of the cases are shown. The summary which follows together with graphs 1 and 2 will give a more rapid survey of the results.

SUMMARY

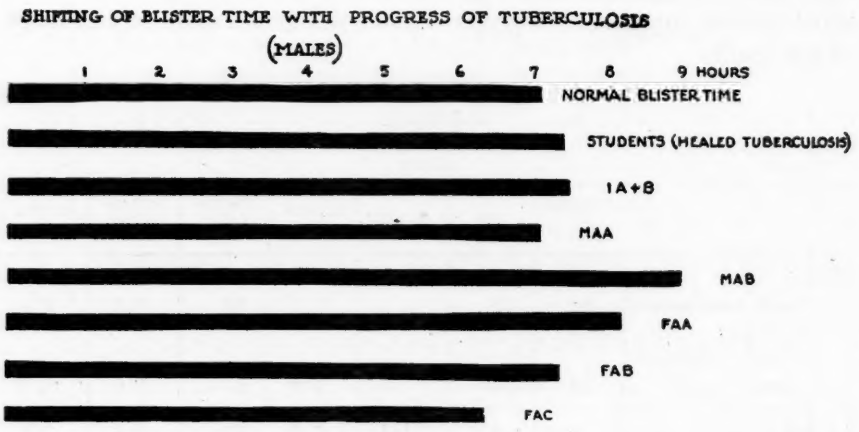
Males

	NUMBER IN GROUP	AGE	WEIGHT	BLISTER TIME	PERMEABILITY RATIO	INFLAMMATORY INDEX	POSITIVE SPUTUM
Controls:							
Medical students...	66	25		7.1	68	9.5	1/66
Students with healed tuberculosis (1 open)....	24	24		7.4	67	9.0	1/66
1A and B.....	9	25	144	7.5	69	9.4	2/9
MAA.....	33	33	148	7.1	68	10.1	21/23
MAB.....	11	29	140	9.0	68	8.5	8/11
FAA.....	15	34	140	8.2	70	9.2	12/15
FAB.....	27	35	122	7.4	73	10.1	27/27
FAC.....	9	31	110	6.4	73	11.5	8/9
Females							
1A.....	22	22	121	6.7	69	10.8	1/22
MAA.....	31	27.7	122	7.0	71	10.2	15/31
MAB.....	17	28	125	7.1	68.5	9.8	14/17
FAA.....	11	30	127	7.0	70	10.7	8/11
FAB.....	15	28	110	7.0	74	10.4	15/15

Totals (males and females)

	NUMBER IN GROUP	AGE	WEIGHT	BLISTER TIME	PERMEABILITY RATIO	INFLAMMATORY INDEX	POSITIVE SPUTUM
A and B	31	22.8			69	10.5	3/31
MAA	64	30.4			68	10.5	36/64
MAB	28	28.4			68	9.0	22/28
FAA	26	32.3			70	9.8	20/26
FAB	42	32.5			73	10.2	42/42
FAC	9	31.0			73	11.5	8/9
Total cases	200						

It will be noted in the summary that, as contrasted with the normal-student material, students with more than the average tuberculous involvement show a slight reduction in permeability and slight prolongation of the blister time, with a resulting lowering of the Inflammatory Index.

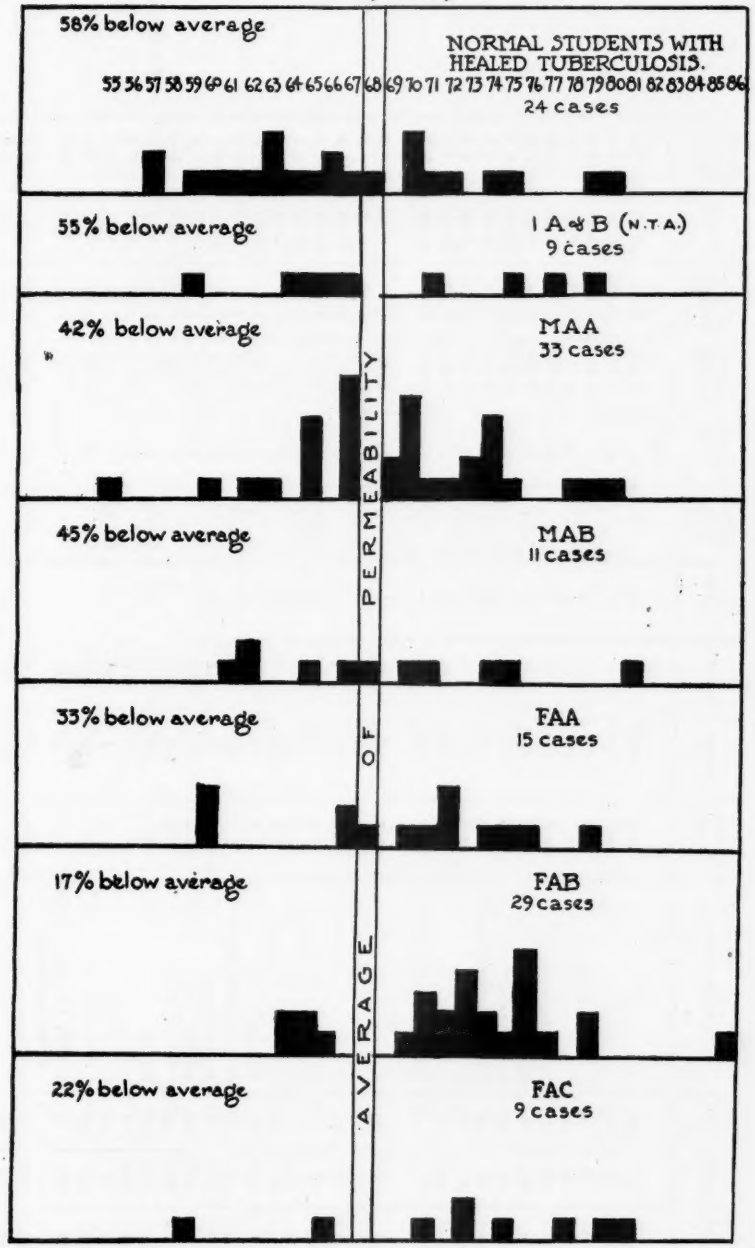


GRAPH 1

Beginning activity in the male group (1A and B) is associated with little change in permeability; with further progress the permeability remains unchanged, but the blister time is prolonged (sympathetic tonus increased) and the Inflammatory Index is lowered (MAA and MAB cases). With far-advanced cases the permeability is increased and the blister time progressively shortened (see graphs 1 and 2).

In the summary of the results in the female group the findings are practically identical, that is, MAB cases having the lowest Inflammatory Index, and the far-advanced cases the higher rate.

SHIFTING OF CAPILLARY PERMEABILITY
WITH PROGRESS OF TUBERCULOSIS
(MALES)



GRAPH 2

TABLE 5

MAA cases (females)

NUMBER	RACE	AGE	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	BLOOD PRESSURE	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	
									hours					
60	C.	32		98.6	100	121	−		8	8.59	5.39	0.61	7.6	
95	W.	14		98	92	99	−		6	7.50	4.69	0.62	10.3	
113	W.	36		97.8	80	126	+		7	9.24	5.90	0.63	9.0	
119	W.	20		98	96	131	+		8¼	8.70	5.53	0.63	7.0	
122	W.	37	Improving	98.2	78	128	−		6	9.24	5.90	0.63	10.5	
101	W.	30	Menstruating*	98.4	98	130	−	122/84	8½	8.80	5.76	0.65	7.6	
110	W.	35	Premenstrual*	98.6	84	141	−		7½	8.16	5.49	0.67	9.5	
120	W.	30	Fibroid; premenstrual	98.6	70	97	+		8½	7.63	5.13	0.67	7.8	
92	C.	27		98.6	84	110	+		10	9.13	6.20	0.68	6.8	
103	W.	30		98.6	96	134	−		8	8.28	5.69	0.68	8.8	
100	W.	32	Adenitis and bone tuberculosis	98.8	90	114	−		7	8.50	5.90	0.69	9.8	
106	W.	23		98.2	80	137	+		7½	8.70	6.00	0.69	9.8	
63	W.	23		98.6	90	118	+		7	7.85	5.49	0.70	10.0	
114	W.	29		98.6	84	153	−		6	7.88	5.53	0.70	11.6	
64	W.	21		98.6	94	128	+	132/76	4	8.70	6.20	0.71	17.0	
112	W.	23		98.6	100	117	+	100/72	7	8.12	5.79	0.71	10.1	
94	W.	36		98.6	100	100	−		9	7.63	5.49	0.71	8.0	
117	W.	36	Fibroid	98.8	82	139	+		6	7.73	5.55	0.71	12.0	
121	W.	32	Often menstruation*	98	88	126	+	106/66	6	7.73	5.55	0.71	12.0	
123	W.	25	Premenstrual*	98.6	98	122	+		7	7.63	5.40	0.71	10.1	
152	W.	30	Fibroid	98.6	84	134	−		6	7.63	5.45	0.71	11.8	
94	W.	36		98.6	100	100	−		9	7.63	5.49	0.72	8.0	
96	W.	53	Fibroid	98	86	132	−	172/94	9	7.52	5.43	0.72	8.0	Wassermann, +
104	W.	29		98	86	118	−		6	8.38	6.10	0.72	12.0	
116	W.	23		97.8	78	134	+	106/60	7	7.84	5.69	0.72	10.2	
108	W.	27		98	80	118	−		8½	8.28	6.10	0.73	9.1	
98	W.	19	Cavity, left apex; peribronchial fibrosis	98.6	100	110	+		6	7.95	5.91	0.74	12.3	
99	W.	29	Stationary	97.8	80	115	−	118/72	5	8.06	5.90	0.74	14.8	
118	W.	23		99.2	90	125	+		6	7.85	5.87	0.74	12.0	
93	W.	33	Old pleurisy; fibroid	98.6	80	126	−		6	8.06	6.06	0.75	12.5	

97	W.	28		98.2	86	140	+	138/72	6	7.96	6.11	0.76	12.6	
107	W.	19	During menstruation;* fibroid	98.8	100	113	−		6	7.63	5.90	0.77	12.8	
111	W.	19	Improved; right base; pleurisy	98.6	90	128	−		7½	8.06	6.30	0.78	11.1	
105	W.	19		98.6	86	103	+		6	8.50	6.70	0.79	13.1	
102	W.	22		98.2	80	128	−		9	7.86	6.30	0.80	8.8	
109	W.	22	Slight activity	99	86	135	+		6	7.70	6.50	0.84	14.0	
Averages.....		27.7				122			7			0.71	10.2	

Total cases, 31.

* Menstrual cases not included.

TABLE 6

MAB cases (males)

NUMBER	RACE	AGE	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	BLOOD PRESSURE	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	
									hours					
200	W.	33	Inactive	98	80	135	+		7	8.60	5.29	0.61	8.7	
55	W.	22		98.8	100	133	−		9	8.50	5.30	0.62	6.8	
70	W.	39	Fibroid	97.8	82	144	−	100/80	9	8.28	5.20	0.62	6.6	Wassermann, +++
72	W.	55	Diabetes; goitre	98.6	94	133	+	110/70	7½	8.70	5.70	0.65	8.6	Albumin and sugar in urine
198	W.	23		98	80	133	+		8	8.70	5.90	0.67	8.3	
199	W.	19		98.4	78	171	−		7½	8.18	5.60	0.68	9.0	
58	W.	41	Fibroid	98.6	70	126	+		25	8.20	5.66	0.70	2.8	Wassermann, ++++
201	W.	26	Improved	98	88	129	+		6	8.10	5.80	0.71	11.8	
197	W.	31	Improved	98	120	168	+		7½	8.70	6.50	0.74	9.8	
73	W.	18		98	84	120	+	118/70	6	8.31	6.30	0.75	12.5	
196	W.	22	Improved	98	84	150	+*		8	8.06	6.60	0.81	10.1	
Averages.....		29				140			9			0.68	8.5	

Total cases, 11.

* Antiformin.

TABLE 7

MAB cases (females)

NUMBER	RACE	AGE	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	BLOOD PRESSURE	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	
									hours					
140	W.	18		98.6	90	122	+		6	8.96	5.09	0.56	9.3	
54	W.	35		100	102	105	+		5	9.55	5.70	0.60	12.3	
56	W.	20		99.6	90	122	+		5	8.28	5.23	0.63	12.6	
127	W.	28		99.2	80	121	+	110/86	7	7.85	5.09	0.64	9.1	
57	W.	25		99	104	116	−		8½	8.29	5.90	0.66	7.7	
141	W.	30		98.6	74	131	+		8½	8.28	5.50	0.66	8.2	
128	W.	31		98.2	100	155	+	102/66	7	7.41	5.09	0.68	9.7	
135	W.	39	Fibroid	98.4	92	138	−		8	7.75	5.29	0.68	8.5	
125	W.	48		98.4	92	155	+		8½	8.70	6.13	0.70	8.2	
129	W.	20		98.2	100	138	+	116/68	7	8.42	5.91	0.70	10.0	
134	W.	22	Menstruating;* mitral regurgitation; pleural adhesions	98.8	116	125	+	96/58	6	7.85	5.60	0.71	11.8	
138	W.	40	Menstruating*	97.6	90	106	−		6	8.92	6.40	0.71	11.8	
59	W.	33		98.6	90	132	−		7	8.28	6.00	0.72	10.2	
124	W.	21		98.6	84	106	+	122/86	8½	7.30	5.29	0.72	8.4	
131	W.	22		99.4	98	129	+	130/88	8½	8.55	6.20	0.72	8.4	Circumscribed hydrothorax
126	W	33		99	100	132	+		7½	8.62	6.30	0.73	9.7	
136	W.	25	Menstruating*	97.6	98	66	+	110/82	4	8.16	6.06	0.73	18.0	
139	W.	33	Second day of menstruation;* myocarditis	98.6	80	135	−		6	7.84	5.80	0.73	12.1	
132	W.	20	Menstruating;* fibroid; tuberculous salpingitis	99.2	98	97	−	96/62	8½	6.86	5.09	0.74	8.7	
130	W.	22		90.1	108	104	+	112/58	7	7.30	5.50	0.75	10.7	
133	W.	42	Stationary	97.4	88	120	+	118/64	6	8.76	6.62	0.75	12.5	Wassermann, +++
137	W.	21	Fibroid	98	84	109	+	100/62	6½	8.06	6.10	0.75	11.5	
Averages.....		28				125			7.1			68.5	9.8	

Total cases, 17.

* Menstrual cases not included.

TABLE 8

FAA cases (males)

NUMBER	RACE	AGE	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	BLOOD PRESSURE	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX
									hours				
37	W.	65		98.8	82	127	−		11	8.60	5.20	0.60	5.4
38	W.	23	Pleuritic adhesions	98.8	102	140	+		12	6.40	3.86	0.60	5.0
39	W.	43		98.8	98	143	+		11	8.70	5.30	0.60	5.4
44	W.	26		98.6	90	141	+		7	7.70	5.90	0.67	9.5
45	W.	22	Open cavity in apex; lower part collapsed	98.6	92	130	+	100/76	7	9.56	6.40	0.67	9.5
46	W.	32	Spontaneous collapse; pleurisy with effusion now pneumothorax	98.6	100	153	+		9	8.49	5.80	0.68	7.7
47	W.	44		100	102	165	+		10	9.77	6.91	0.70	7.0
48	W.	30		96.8	100	147	+		11	8.70	6.20	0.71	6.4
49	W.	35		97	88	132			6	8.70	5.90	0.72	12.0
146	W.	46		98	86	158	+	95/65	7	8.28	6.00	0.72	10.0
148	W.	26		98.6	84	−	+	120/80	4	8.71	6.30	0.72	18.0
50	W.	37	Tuberculous pleurisy and pneumothorax last year; now tuberculous pleurisy	101	100	128	+	110/70	6	7.50	5.60	0.74	12.3
145	W.	38	Peribronchial pneumonia; laryngitis; died	101.6	118	158	+		6	7.00	5.29	0.75	12.0
51	W.	19	Cavitation	98.8	106	102	−		9	8.28	6.20	0.76	8.4
147	W.	33	Old pleurisy; cavitation	98.8	94	−	+		8	8.92	7.05	0.79	9.8
Averages.....		34				140			8.2			0.70	9.2

Total cases, 15.

TABLE 9

FAA cases (females)

NUMBER	RACE	AGE	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	BLOOD PRESSURE	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	
									hours					
40	W.	31		98.8	70	138	+		4	10.30	6.62	0.64	16.0	
41	W.	30		98.6	96	95	+	120/80	9	8.57	5.53	0.64	7.1	
42	W.	55	Diabetes	98.6	80	166	+	128/76	8½	10.30	6.77	0.65	7.6	Wassermann, A. C.
144	W.	42		98.6	88	146	+		7	8.28	5.49	0.66	9.4	
143	W.	32	Mitral stenosis	98.6	80	118	+		10	9.35	6.30	0.67	6.7	Albumin in urine
43	W.	15	No activity	99.2	110	92	−		8½	8.05	5.45	0.67	7.8	
142	W.	31		97.4	86	160	+		6	8.28	5.69	0.68	11.3	
153	W.	25	Inactive	97.8	90	135	−		6	7.85	5.70	0.72	12.0	
52	C.	19		98.6	120	118	+	140/90	5	8.70	6.65	0.76	15.2	
53	W.	29	Healed cavity at apex	98.6	84	155	+		5½	7.30	5.60	0.76	13.0	
154	W.	21	Pregnant now	98.6	90	73			7	6.37	5.09	0.80	11.4	
Averages.....		30				127			7			0.70	10.7	

Total cases 11.

TABLE 10

FAB cases (males)

NUMBER	RACE	AGE	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	BLOOD PRESSURE	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	
									hours					
4	W.	29	Pneumothorax	99.8	106	148	+		9	8.92	5.70	0.64	7.11	
202	W.	21	Exudative	100	136	106	+		6	8.80	5.69	0.64	10.60	Albumin, trace
6	W.	57	Cavity; tuberculous orchitis; thoracoplasty	97.6	90	122	+		7½	6.35	4.10	0.65	8.66	Wassermann, +
7	W.	22	Laryngitis, slight effusion; pleurisy	101	112	103	+		6	5.90	3.86	0.65	10.80	
8	W.	37	Cavitation; laryngitis	98.6	94	102	+		7	8.90	5.90	0.66	9.40	
11	W.	23	Thoracoplasty, right side	99.5	102	124	+		16	8.28	5.80	0.70	4.30	Albumin, trace
13	W.	42	Laryngitis	98.8	104	129	+		7	7.97	5.70	0.71	10.10	
14	W.	22	Multiple cavitation	98.2	100	106	+	85/60	7	7.55	5.40	0.71	10.10	
204	W.	20	Ulcerative laryngitis	101.6	100	110	+		9	7.55	5.40	0.71	7.80	
15	C.	36	Pneumothorax treatment	97.8	98	183	+		11	9.25	6.70	0.72	6.50	
16	W.	35	Cavitation; left thoracoplasty	97	110	118	+		7½	8.28	5.90	0.72	9.60	
17	W.	24	Cavitation	98	98	118	+		8	9.35	6.91	0.73	9.10	
18	W.	31		99.2	94	117	+		10	7.80	5.70	0.73	7.30	
20	W.	38	Fibroid pleurisy; left ethmoiditis	99	84	128	+		8	7.20	5.29	0.73	9.10	
203	W.	15		97	110	112	+	100/65	6	8.40	6.20	0.73	12.10	
22	W.	41	Cavitation; fibroid	99.5	97	102	+		7½	8.49	6.30	0.74	9.80	
23	W.	33		98.6	84	141	+	110/85	6	8.49	6.30	0.74	12.30	
25	W.	35	Pleural adhesions and effusion	98.8	100	163	+		7½	8.38	6.30	0.75	10.00	
27	W.	52	Chronic fibroid; mitral regurgitation	98.2	84	119	+		9	7.20	5.50	0.76	8.44	
28	W.	45		99	86	118	+		10½	7.95	6.10	0.76	7.20	
29	W.	34	Upper right fibrosis; toxic myocarditis	99.6	100	108	+		6	8.00	6.10	0.76	12.60	
149	W.	27	Cavitation	102	100	120	+	100/75	6	7.41	5.69	0.76	12.70	
150	W.	48	Cavitation	102.6	120	−	+		6	7.00	5.69	0.76	12.60	
30	W.	49	Fibrocaseous right upper; left upper fibroid	98	80	119	+	106/72	6½	9.23	7.11	0.77	11.80	
31	W.	51	Cavitation	99.4	96	125	+	95/60	6½	9.23	7.11	0.78	10.40	
32	W.	67		98.6	84	120	+		7	7.60	5.90	0.78	11.10	
36	W.	24	Marked pneumofibrosis; tuberculous otitis media	103	140	120	+	125/80	7	6.35	5.49	0.86	12.20	
Averages.....		35				122			7.4			0.72	10.10	

Total cases, 27.

TABLE 11

FAB cases (females)

NUMBER	RACE	AGE	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	BLOOD PRESSURE	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	
									hours					
5	W.	28	Tuberculous enteritis	98.6	120	109	+		7	7.63	4.89	0.64	9.14	
158	W.	19	Fibroid	98.4	104	123	+		6	8.06	5.29	0.65	10.80	
9	W.	30	Cavitation; tuberculous enteritis	98.2	118	95	+		7½	8.34	5.69	0.68	9.00	
10	W.	37		100.2	102	106	+		8	7.85	5.40	0.69	8.60	
12	W.	14	Increasing symptoms of toxicity	98.6	90	81	+		6	7.85	5.50	0.70	11.60	
19	W.	25	Cavitation	103	130	91	+	90/62	6	5.822	4.272	0.73	12.10	
21	W.	38	Fibroid type	101	100	108	+		7	6.55	4.89	0.74	10.50	
24	W.	20	Calculi in right kidney	99	100	140	+		10	8.60	6.50	0.75	7.50	Albumin in urine, +; blood in urine, +
26	C.	18	Pleural adhesions; hilum fibrosis	101	120	119	+		7	7.20	5.49	0.76	10.80	
155	F.	38	Ulcerative type; pneumothorax case	97.4	94	94	+		7	6.61	5.03	0.76	10.80	Albumin in urine
33	W.	32	Chronic suppurative otitis media	100.8	102	119	+		6½	7.41	5.80	0.78	10.40	
157	W.	29	Expects to menstruate today, but is bleeding from nose	98	80	85	+		7	8.38	6.55	0.78	11.10	
34	W.	39	Cerebral hemorrhage, 3 years ago; hemiplegia and aphasia	98.8	106	119	+	98/62	7	7.20	5.69	0.79	11.20	
156	W.	24	Ulcerative type; tuberculous laryngitis and enteritis	99	112	105	+	106/78	7	6.76	5.40	0.80	11.40	
35	W.	31	Acute laryngitis; sanocrysin treatment	100.6	128	150	+	110/68	7	6.98	5.90	0.84	12.00	Albumin in urine, trace
Averages.....		28				110			7			0.74	10.40	

Total cases, 15.

TABLE 12
FAC (males)

NUMBER	RACE	AGE	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	BLOOD PRESSURE	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	
									hours					
210	W.	33	Tuberculous peritonitis and enteritis; enlarged liver; ascites	98.6	88	140	+		12	5.67	3.34	0.59	4.9	Wassermann, ++++; albumin in urine, +
205	W.	26	Pleurisy with effusion; mitral regurgitation; endocarditis and myocarditis	101	110	135	+		6	6.12	4.06	0.66	11.0	
3	W.	46	Cavitation	101	100	106	+	105/70	6½	8.70	6.30	0.71	10.9	
2	W.	43	Collapse of left lung	99	90	−	+		5	6.12	4.40	0.73	14.6	Wassermann, +++
107	W.	19		99	108	110	+	95/60	6	6.12	4.47	0.73	12.1	Casts and albumin in urine
1	C.	35	Collapse of left lung; cavitation.	101	118	130	+	124/84	6	6.98	5.29	0.75	12.5	
206	C.	10	Generalized miliary tuberculosis; peritoneal and meningeal tuberculosis	99.2	100	66	−		7	6.31	8.06	0.78	11.1	
208	W.	38	Spontaneous pneumothorax	99.8	118	98	+	90/60	6	6.98	5.55	0.80	13.3	
209	W.	28	Pleurisy with effusion	98.6	96	98	+	95/65	6	8.06	6.60	0.81	13.5	
Averages.....		31				110			6.4			0.73	11.5	

Total cases, 9.

TABLE 13

Cases with evidence of clinical activity under one year

NUMBER	RACE	AGE	DIAGNOSIS	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	FIRST TOOK SICK	LAST BREAKDOWN	TUBERCULOSIS IN FAMILY	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	DARANYI
												hrs.					
1	W.	21	IA	Improved	98	72	152	−	8 months ago	8 months ago	Negative	6	8.20	6.20	0.75	12.5	
7	W.	16	IA	Slightly active	99.6	90	128	−	Cold and cough 3 years ago	February, 1926	Negative	7	7.85	6.10	0.77	11.6	Negative
10	Y.	23	MAA	Active	97.8	92	106	+	Cough, October, 1925	Same		12	7.63	5.40	0.70	5.8	++++
11	W.	29	MAA	Fibroid	98.2	74	149	+	Influenza, 1918	February, 1926	Aunt died	6	8.92	6.00	0.67	11.1	++++
18	W.	19	MAA	Improving	98	80	152	−	Cough, 6 months ago	January, 1926	Negative	6	8.49	5.69	0.67	11.1	++++
23	W.	29	MAA		97.6	70	180	−	Influenza, 1919	March 8, 1926; pleurisy and cough	Grandfather died	6½	8.28	4.60	0.55	8.4	+++
26	C.	40	MAA	Active	92.2	86	157	+	Influenza, 1921; cough	November, 1925	Negative	10	8.14	5.98	0.73	7.3	++++
30	W.	26	MAA	Slightly active	98.2	80	170	−	October, 1925	November, 1925	Negative	8	8.70	6.10	0.70	8.7	++++; Wassermann, A. C.
42	W.	26	MAB		98	88	129	+	October, 1925	March, 1926	Negative	6	8.10	5.80	0.71	11.8	+++
44	W.	15	FAB		97	110	112	+	August, 1925	1925	Negative	6	8.40	6.20	0.73	12.4	++++
45	W.	20	FAB	Ulcerative laryngitis	101.6	100	110	+	July, 1925, cough	Pneumonia, September, 1925; sick since	Negative	9	7.55	5.40	0.71	7.8	+++
47	C.	10	FAC	Tuberculous peritonitis; miliary pulmonary tuberculosis	99.2	100	66	−	Pneumonia, 1925	April 27, 1926	Negative	7	6.31	8.06	0.78	11.1	++++; Pirquet +; albumin in urine
49	W.	38	FAC	Spontaneous pneumothorax	99.8	118	98	+	Pneumonia, 1915	October, 1925; bloody sputum	Negative	6	6.98	5.55	0.80	13.3	++
50	W.	28	FAC	Pleurisy with effusion	98.6	96	98	+	Hemoptysis, 1 year ago	Pneumonia, March, 1926	Brother died	6	8.06	6.60	0.81	13.5	
															R =	R/T =	
Average...		25													0.72	10.2	

Total cases, 14.

TABLE 14

Cases with evidence of clinical activity from 1 to 5 years

NUMBER	RACE	AGE	DIAGNOSIS	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	FIRST TOOK SICK	LAST BREAKDOWN	TUBERCULOSIS IN FAMILY	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	DARANYI
												hrs.					
3	W.	40	IA	Improved	98	80	175	+	2½ years ago	Hemoptysis, 1 year ago	Negative	7½	8.57	5.49	0.64	8.5	
4	W.	21	IA		98	82	158	−	May, 1925	May, 1925	Sister died	9	7.73	4.57	0.59	6.5	Negative
5	W.	19	IA		97.6	84	134	−	Pneumonia, March, 1925	June, 1925	Negative	6	7.10	5.09	0.71	11.8	
8	W.	24	IB		98.6	74	140	−	1 year ago	2 months ago	Negative	8½	8.16	5.33	0.65	7.6	+
9	W.	33	IB	Fibroid pleurisy	98.8	100	112	+	Intestinal obstruction, 1925	1 year ago	Negative	8	8.16	5.49	0.67	8.3	−
14	W.	21	MAA		97.8	72	166	−	Influenza, March, 1925; cough	Same	Brother died	6	8.38	5.90	0.70	11.6	+++; Wassermann +
15	W.	28	MAA		97.8	72	135	+	Influenza, 1918	2 years ago	Negative	6	8.70	6.50	0.74	12.3	
16	W.	19	MAA		97.6	80	131	+	Cough 2 years ago	Hemoptysis, May, 1925	Negative	8½	8.28	6.10	0.74	8.7	++++
22	W.	32	MAA	Fibroid	97.8	82	158	+	1 year, 4 months ago	1 year ago; pleurisy and cough	Negative	6½	7.95	5.09	0.64	9.8	−
28	W.	17	MAA		97.2	84	102	+*	1923	1923	Negative	6	8.28	6.50	0.78	13.0	
29	W.	66	MAA	Improved	98	70	133	+	1925. Pneumonia 30 years ago	1925	Negative	6	8.06	5.20	0.64	10.6	++++
32	W.	49	MAA	Fibroid	98	88	120	−	3 years ago	2 years ago	Negative	6	7.47	5.40	0.72	12.0	
34	W.	23	MAA		98.2	76	132	+	Hemoptysis, 1924	1924	Negative	6	7.99	6.30	0.79	13.1	
35	W.	28	MAA	Fibroid	97.8	80	180	+	Influenza, 8 years ago. Cough	Hemoptysis, 15 months ago	Child died	6	8.92	6.00	0.67	11.6	++
36	W.	42	MAA	Stationary	98.4	78	166	+*	Influenza-pneumonia 1922	1922	Negative	8	7.20	5.09	0.70	8.7	−
37	W.	22	MAB		98	84	150	+*	Pleurisy and cough, 4 years ago	Hemoptysis, 1925	Negative	8	8.06	6.60	0.81	10.1	++++
40	W.	19	MAB		98.4	78	171	−	January, 1925	March, 1925	Sister died	7½	8.18	5.60	0.68	9.0	+++
43	W.	21	FAB	Exudative	100	136	106	+	1925; cough	Persistent cough, 1925	Negative	6	8.80	5.69	0.64	10.6	++++; albumin in urine
13	W.	26	MAA	Active	98.2	78	120	+	8 years ago	8 months ago	Negative	6	8.50	6.30	0.74	12.3	++++

27	W.	38	MAA	Improved	98	72	168	+	Pneumonia, 7 years ago; hemoptysis, May 10, 1924	December, 1925	Negative	11	7.84	4.76	0.60	5.4	−
48	W.	19	FAC		99	108	110	+	Cough, September, 1924	September, 1925	Father died	6	6.12	4.47	0.73	12.1	++++; casts and albumin in urine
39	W.	23	MAB		98	80	133	+	Pleurisy, 1923; influenza, 1924	July, 1925	Negative	8	8.70	5.90	0.67	8.3	
Average...		28													R = 0.69	R/T = 10.0	

Total cases, 22.
* Antiformin.

TABLE 15

Cases with evidence of clinical activity of more than 5 years

NUMBER	RACE	AGE	DIAGNOSIS	CLINICAL NOTES	TEMPERATURE	PULSE	WEIGHT	SPUTUM	FIRST TOOK SICK	LAST BREAKDOWN	TUBERCULOSIS IN FAMILY	BLISTER TIME	SERUM PROTEIN	BLISTER PROTEIN	RATIO	INFLAMMATORY INDEX	DARANYI
												hrs.					
2	W.	21	IA		98.6	88	108	−	6 years ago	3 months ago	Negative	7	7.41	5.90	0.79	11.2	
6	W.	35	IA	Inactive	98.2	84	142	−	Pleurisy, 1913	1915	Sister died	9	8.49	5.60	0.66	7.3	
17	C.	59	MAA	Mitral regurgitation	96.8	78	153	+	Influenza, 1920	February, 1922	Negative	6	9.13	5.69	0.62	10.3	Wassermann, ++
19	W.	28	MAA	Fibroid	97.4	78	130	+	1919	1920	2 brothers and father died	10	7.20	4.57	0.63	6.3	
20	W.	51	MAA	Fibroid	97.6	78	183	−	6 years ago	Hemoptysis, 1925	Negative	6	7.95	5.49	0.69	11.5	
38	W.	31	MAB		98	120	168	+	Bronchitis since 10 years of age	Spitting blood, 1918	Negative	7½	8.70	6.50	0.74	9.8	Wassermann, A. C. +; Wassermann, ++++; albumin, ++++
51	W.	33	FAC	Tuberculous peritonitis and enteritis	98.6	88	140	+				12	5.67	3.34	0.59	4.9	
12	W.	35	MAA		96.8	76	212	−	1914; cough continuously for 3 years	Hemoptysis, 1925	Negative	10	8.60	5.49	0.64	6.4	−
21	W.	23	MAA	Stationary	98.6	76	141	+	Influenza 8 years ago	7 months ago	Negative	8½	8.92	6.20	0.70	8.2	++
25	W.	41	MAA	Inactive	98.6	76	146	+	Hemoptysis 20 years ago	1926	Aunt died	6½	7.06	4.78	0.67	10.3	−
31	W.	46	MAA	Fibroid	97.4	82	163	−	6 years ago	3 years ago	Negative	6	8.06	5.40	0.67	11.1	
33	W.	41	MAA		98.6	84	134	+	5 years ago	1 year ago	Negative	9	8.81	6.60	0.75	8.3	++++
41	W.	33	MAB	Inactive	98	80	135	+	Cough, 1918; influenza, 1926	1926	Negative	7	8.60	5.29	0.61	8.7	
46	W.	26	FAC	Pleurisy with effusion	101	110	135	+	Pleurisy, 10 years ago	February, 1926	Negative	6	6.12	4.06	0.66	11.0	++++
24	C.	31	MAA	Stationary	98.6	68	178	+	Never sick	6 months ago, sputum positive for tubercle bacilli	Child died	6	8.88	5.80	0.69	11.5	++
Average...		35													R = 0.67	R/T = 9.0	

Total cases, 15.

Interpretation: In view of our previous studies we conclude from these results that the incipient tuberculosis patient reacts (as far as a non-specific irritant (cantharides) is concerned) with very little change in the endothelium or tonus of the arteriole. We do not wish to imply that this is evidence of the functional stability of these structures. The nervous element in vegetative control may be quite unstable, as we know from clinical symptoms. But the capillary endothelium and the arteriole react within normal limits. The reversibility is not impaired, that is, there is here no evidence of fatigue.

With moderately advanced cases we find no great change in permeability but a distinct lengthening of the blister time, with a resulting lowering of the Inflammatory Index. In broad terms this must mean an increase in the sympathetic tonus of the arteriole. This group of patients will include recent cases that are stationary, as well as many old fibrous cases. They include, in general, the cases that are relatively resistant; that is, with uninjured endothelium and increased sympathetic tonus.

The far-advanced cases, on the other hand, bring the reverse of this orientation. The endothelium has been injured (fatigued), and it begins to be more permeable. The blister time becomes shortened (Inflammatory Index rises), and we have less sympathetic or relatively more parasympathetic effect.

Acute exudative cases, as we have shown elsewhere, even with only minor parenchymal findings, have permeable capillaries, and obviously this course of the disease may acutely supervene with any stage of the classification that we have used.

Relation to Duration of Disease: In an analysis made on the basis of 50 male cases, in which the classification has been made into three groups according to the duration (under one year, 1 to 5 years, and more than 5 years), the following summaries can be presented:

	CASES	AVERAGE AGE	PERMEABILITY	INFLAMMATORY INDEX
		Under 1 year		
1	14	25	72	10.2
		1–5 years		
2	22	28	69	10
		More than 5 years		
3	15	35	67	9

No.	Perm. Ratio	Blister Time	Tuberculin Reaction 24 hrs.	48 hrs.	72 hrs.	History	Roentgen
4	57	7					Moderate Hilum shadows. Exaggeration of linear markings. Moderate Ca. of hilum.
5	57	11				Brother	Moderate calcification of hilum. Hilum density average. Parenchyma unaltered.
6	57	16					Mod. calcification of the hilum. Little marking.
10	60	9				Possibly	Marked calcification of costal cart. Hilum normal density. Little calcific.
12	61	8-1/2					Hilum and calcification sl. increased. Parenchyma normal.
13	61	7				Family	Old healed pulmonary. Hilum calcific. Moderate Ghon R.L. Linear markings exaggerated.
17	63	7				Father	Old R.L., with many small areas. Sl. increase of hilum density. Linear markings normal.
19	63	7					Possibly old pulmonary. Mod. calcification of the hilum. Some increase of linear markings.
22	64	11					Fairly heavy hilum shadows and calcific. Linear markings increased.
23	64	5				Family	Old Pulmonary. Ghon R.L. Hilum more than average density. Linear markings only slightly increased.
25	65	6					Increased hilum shadows, very little calcific. Linear markings normal.
26	65	8					Hilum slightly increased density. Calcific. normal. Linear markings slightly increased.
27	65	9-1/2				Family	Hilum normal. Calcific. of hilum normal. Linear markings normal.
28	65	5-1/2					Hilum normal. Linear markings normal.
29	65	6-1/2					Hilum shadows normal. Linear markings sl. increased.

GRAPH 3. RELATION OF PERMEABILITY RATIO IN NORMAL STUDENTS TO TUBERCULIN REACTION

31	66	8				Normal hilum. Little calcification. Slightly exaggeration linear markings.
32	66	6-1/2				Active, soft infiltration Linear markings exaggerated. Mod. calcification of the hilum.
34	67	6-1/2				Active, soft infiltration of U.R. Old adherent R. Diaphragm. Little Ca. of the hilum.
37	68	6			Family	Mod. calcification of the hilum. Lin. markings mod. exaggerated.
38	69	6-1/2				Mod. hilum shadow. Linear markings normal.
41	70	9				Normal. Little calcific. of the hilum. Markings normal.
42	70	7-1/2			Family	Normal. Sl. hilum calcific.
43	70	6				Increased density and calcific. of hilum. Exaggerated markings of parenchyma.
44	70	10-1/2				Healed Upper Pulmonary.
50	73	10-1/2			Mother?	Hilum normal. Markings sl. exaggerated.
53	74	6				Mod. hilum shadow. Linear markings normal.
54	74	6				Sl. increase hilum shadow Little calcification.
55	74	4				Normal.
57	74	4				Old healed pulmonary. Calcification in parenchyma.
59	75	4				Ghon. Moderate hilum calcific. Linear markings mod. increased.
60	76	6-1/2				Normal.
63	79	7-1/2				Old R.U. Parenchymal. Probably inactive.
66	84	7				Normal hilum shadows and calcification. Mdd. exaggeration of linear markings.

GRAPH 3 (*Concluded*)

In these groups the first will contain cases of varied prognosis, in the second group chronicity becomes apparent, and in the third we deal definitely with resistance that has been demonstrated by the duration of the disease. The less resistant material has been eliminated by death.

No.	Age	Perm. Ratio	Blister Time	Tuberculin Reaction 24 hrs.	Tuberculin Reaction 48 hrs.	History	Menst. Relation	Inflammatory Index
1	20	81	3 hrs.	●	●	None	PRE.M.	27.0
2	19	81	4			Family	PRE.M.	20.2
3	18	80	3	●	●	None	PRE.M.	27.0
4	20	79	5	●	●	None	2nd day	15.8
5	21	79	8	●	●	None	INTER. M.	10.0
25	33	79	4-1/2			None	INTER. M.	17.5
6	19	78	3	●	●	None	PRE.M.	26.0
8	26	77	3	●	●	None	PRE.M.	26.0
7	21	76	3-1/2	●	●	Family	PRE.M.	21.7
9	19	76	3-1/2	●	●	None	PRE.M.	21.7
10	22	76	1-1/2	●	●	None	PRE.M.	50.0
11	22	75	3	●	●	Family	INTER.M.	25.0
12	19	75	5	●	●	None	INTER.M.	15.0
13	21	74	2	●	●	None	INTER.M.	37.0
14	18	74	4	●	●	None	INTER.M.	18.0
15	22	74	3	●	●	None	INTER.M.	25.0
16	32	73	8	●	●	None	INTER.M.	9.1
17	19	71	8	●		None	PRE.M.	9.0
18	29	70	4	●		None	PRE.M.	17.5
24	19	70	3-1/2	●	●	None	INTER.M.	20.0
19	19	70	7-1/2	●	●	None	INTER.M.	9.3
20	19	67	8	●	●	None	INTER.M.	8.3
21	18	65	4-1/2	●	●	None	INTER.M.	14.4
22	19	62	4	●	-	None	PRE.M.	15.5
23	31	62	7	●	●	None	INTER.M.	9.0

GRAPH 4. RELATION OF NONSPECIFIC INFLAMMATORY INDEX AND PERMEABILITY RATIO TO TUBERCULIN REACTION

The increase in the sympathetic orientation of the skin is obvious, both in the lessened capillary permeability and in the lowering of the Inflammatory Index. Here again sympathetic tonus and resistance parallel each other.

RELATION OF BLISTER TEST TO TUBERCULIN REACTION

To determine whether there might be any correspondence between sensitiveness to tuberculin and the relative response of the capillaries to cantharides, we carried out Pirquet tests on normal student material and on the group of nurses which had been studied in connection with menstruation. In graphs 3 and 4 it will be observed that there is no evident relation. Both groups have been arranged in an order of degree of permeability as determined by the blister, while the 24- and 48-hour tuberculin reactions are indicated by the relative size of the black areas.

RESISTANCE IN TERMS OF THE VEGETATIVE SYSTEM

Examined from the simplest point of view, resistance to tuberculosis means complete walling off from general tissue activity, that is, impermeability: anatomically, in the sense of a complete connective-tissue encapsulation; and functionally in the sense that there shall be no exchange of products between the focus and the normal tissues. The converse means the enhanced opportunity for the absorption of bacillary and tissue debris, and the dissemination of the virus.

The exchange is mediated through alterations in the endothelium of the surrounding capillaries (blood and lymph capillaries). Substances that stimulate and dilate capillaries, with incidental increase in permeability, must be potentially injurious. Substances that fatigue the capillary (with delay in its reversibility) must be harmful without qualification. Substances that make the capillary less permeable must be essentially beneficent.

Expressed in terms of the vegetative apparatus, the parasympathetic status corresponds with the former condition. The capillary endothelium is stimulated, that is, becomes more permeable, calcium leaves the cell, and there is an increased acidity of the tissue. Clinically, we associate it with exudative and progressive tuberculosis, with the increase of parasympathetic symptoms (instability of the pulse-rate, lowering of the blood-pressure, tendency to sweat, low blood sugar, lability of the body temperature, increased catabolism).

The status associated with lessened permeability of the capillary we designate as sympathetic. The arteriole tonus is high, the blood sugar (liver function) normal, the tissues bind calcium, the reaction is toward the alkaline side.

In recent years this concept has been developed by a number of ob-

servers, partly on the basis of clinical observation, partly as a result of biochemical studies in the laboratories. Guth, in particular, has sought to demonstrate that benign tuberculosis is associated with increased or normal sympathetic tonus while progressive tuberculosis means an increase of the parasympathetic. His most interesting papers are too extensive to review at this time (31): Kading (32) and Glaser (33) have reached similar conclusions.

CONCLUSIONS

1. By means of the blister method definite alterations in capillary permeability and the inflammatory response of the skin can be determined in different clinical stages of tuberculosis. Capillary permeability remains practically constant in the "incipient" and "moderately advanced" stages, but the blister time becomes prolonged and the "inflammatory index" consequently smaller. In the "far advanced" stage there are a progressive increase in capillary permeability and a shortening of the blister time. This latter condition we associate with an increased parasympathetic status of the vegetative system. In exudative cases the permeability is markedly increased.

2. Examined on the basis of duration of disease, those instances of longest duration have the lowest index of permeability and lowest Inflammatory Index.

3. There is no evident relation of this response to cantharides and the tuberculin reaction.

3. We associate the lowered resistance incident to season, menstruation, parturition, etc., with the change in the vegetative status of the organism (parasympathetic), of which the change in permeability is a manifestation. On the other hand, the increase in resistance (relative benignancy), demonstrated for senility and for arteriosclerotic nephritis, may be associated with the relatively sympathetic status of such individuals.

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A NONPROTEIN ANTIGEN OF THE TUBERCLE BACILLUS[1]

MAX PINNER[2]

Ever since Bang and Forssman's first publication on heterogenetic hemolysins, produced by organ lipoids, and since Much and his school have emphatically claimed the existence and significance of antibodies not only against lipoids but against neutral fats as well, there has been discussion of the question of whether nonprotein substances may be genuine antigens. Much and his co-workers, Stuber and K. Meyer, in Germany, Embleton and Thiele in England, Bocquet and Nègre in France, Jobling, and Dienes and his associates in the United States, have presented much evidence in favor of this view. To review the whole question would mean to review the better part of the work on Wassermann antigens, on partial antigens, on complement fixation in tuberculosis and on nonspecific fixations, on nonspecific stimulation of antibody production, on typhoid agglutinins and on a few more immunological problems. Excellent reviews of the whole question can be found in Schmidt (1) and in Jobling (2). For the present purpose it may suffice to summarize the situation as follows: The classical school of immunologists have always claimed that any antigenic action displayed by a so called lipoid or fat was due to contamination with proteins. Such an attitude must delay definite decision of the question until far beyond our time, since chemistry has no methods at the present time to effect an *absolute* separation of protein and nonprotein substances from animal or vegetable tissues, or to prove such a separation, if it should by chance be achieved. But, since this question is of fundamental importance, a different approach was attempted.

For the substance discussed here, no claim is made that it is protein-free, but it is accurately determined how much protein it may maximally contain. The antigenic properties of this substance are quantitatively determined. In a simultaneous series of experiments the antigenic properties of the double amount of its possible protein contamination are

[1] Presented at a session of the Pathological Section of the twenty-second annual meeting of the National Tuberculosis Association, Washington, D. C., October 4, 1926.

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determined, using the purest bacillary protein available, and compared with the original substance. It is shown below that the double amount of "pure" protein, which may maximally contaminate the nonprotein antigen, has no appreciable antigenic properties.

The antigen used was, in brief, the alcohol-soluble substance of tubercle bacilli, which proved to be very active in complement fixation, and which, as was found in previous work, increased in activity at every attempt at purification.

A substance is here accepted as antigen only if it produces specific antibodies when injected into a normal animal,—antibodies, with which it will react specifically in test-tube reactions. Substances which react *in vitro* specifically with immune sera, but which do not produce antibodies when injected into normal animals, should not be called antigens, but *haptens*.

METHODS

1. Preparation of the Antigen: Six strains of human and five strains of bovine tubercle bacilli, grown on glycerol-agar (4 to 10 weeks' growth) were dried *in vacuo* at 80° over phosphorus pentoxide to constant weight (11.5 gm.), and then finely ground in an agate mortar. They were then extracted in a Soxhlet apparatus for two hours with acetone dried over calcium chloride. The residue was dried in an incubator at 37° and then extracted with water-free chloroform for two hours; the residue was dried again and extracted for four hours with methyl-alcohol dried over calcium oxide. Two hundred and ninety cubic centimetres of alcoholic extract were obtained, of which 200 cc. were mixed with 100 cc. of freshly redistilled water and evaporated *in vacuo* below 60° to 50 cc. This opaque fluid, which gives a faint ninhydrin reaction, was transferred into dialysis bags of collodion, a few grains of trypsin were added and well mixed, and the mixture was submitted to simultaneous digestion and dialysis against distilled water in an incubator at 37° for 72 hours. The outer water was changed three times in 24 hours. The contents of the bags constitute the finished antigen; 40 cc. were recovered. It will hereafter be called by its protocol number *8*.

2. Chemical Properties: The antigen is a very homogenous, rather stable suspension of pH 6.8. One cubic centimetre contains 5.2 mgm. dried residue, a slightly yellowish amorphous mass. It contains 0.095 mgm. N in 1 cc. (determined by Koch's method). The following protein

reactions were performed on this substance: ninhydrin, biuret, sulphosalicylic acid, glyoxylic acid, xanthoproteic, Millon's. They all were negative. The next step was to determine what amounts of tubercle-bacillus proteins can be detected by these reactions. As test proteins, I used (1) a protein (water-soluble, noncoagulable), labelled KF_3, that Drs. Long and Seibert isolated and purified from tubercle-bacilli broth, and which, as described (Long and Seibert (3)) is a potent tuberculin; and (2) a tubercle-bacillus protein, made by Dr. T. B. Johnson, labelled 304, and with N of 14.38 per cent (4). Table 1 gives the results of these tests.

It was next ascertained that antigen *8* does not contain anything which might prevent any of the protein reactions. A solution of 1:5000 of KF_3

TABLE 1

KF 3 (LONG AND SEIBERT)	BIURET	MILLON'S	XANTHO-PROTEIC	GLYOXYLIC-ACID	NINHYDRIN	SULPHOSALI-CYLIC ACID
1:1000	+	Trace	+	−	−	+
1:2000	+	−	+	−	−	−
1:5000	−	−	+	−	−	−
1:7500	−	−	−	−	−	−
304 (JOHNSON)						
1:1000	+	+	+	Trace	−	+
1:2000	+	−	+	−	−	−
1:5000	+	−	+	−	−	−
1:7500	−	−	−	−	−	−

in *8* gave a positive xanthoproteic test, and a solution of *304* in *8* gave a positive biuret and xanthoproteic test. Similar tests were performed with several other tubercle-bacillus proteins. The results were always essentially the same. It was therefore felt that the conclusion is justified that *8* contains less than 1:5000 protein. All further experiments were made under the assumption that *8* contains 1:5000 protein, or 0.2 mgm. per cubic centimetre.

It may be mentioned here that several batches of this antigen were prepared, occasionally with slight modifications; the end-product had always essentially the same properties.

3. Immunological Properties: The crude alcohol extracts and the partially purified end-products were titrated as antigens in complement fixation.

Technique: Two hemolytic units of sheep amboceptor and two full units of complement were used; the first incubation was for $\frac{3}{4}$ hour at 37°; after addition of sensitized red cells (a 2.5 per cent suspension) the second incubation was $\frac{1}{2}$ hour at 37°. As test-serum the pooled serum of three or four tuberculosis patients, each giving a 4-plus fixation with two different antigens, was used. The so called *range* of an antigen finds its numerical expression by the antigenic quotient, that is, the quotient between anticomplementary and antigenic unit. Table 2 gives the data for three different batches of antigens. This table shows clearly the effect of purification, inasmuch as the antigenic units are significantly smaller ($\frac{1}{2}$ to $\frac{1}{20}$) and the antigenic quotients definitely larger (100 to 400 per cent) in the end-product as compared with the alcoholic extracts. The percentage of protein content is, of course, the smaller according as

TABLE 2

PRODUCT	ANTIGENIC UNIT	ANTIGENIC QUOTIENT	MAXIMAL PROTEIN CONTENT PER ANTIGENIC UNIT	DRY WEIGHT PER 1 CC.
	mgm.		*mgm.*	*mgm.*
Alcoholic Extract C	0.0008	100		1.7
Purified C	0.000475	200	About 0.000095	0.95
Alcoholic Extract 8	0.00492	50		4.92
Purified 8	0.00052	200	0.0000208	5.2
Alcoholic Extract 11	0.0051	20		2.56
Purified 11	0.000225	50	0.0000173	2.75

the final product is more concentrated. The antigenic units are found to be around one-half of 0.001 mgm. The best protein antigens that I have had an opportunity to examine have an antigenic unit of about 0.01 to 0.02 mgm. Dienes, *et al.*, worked with tuberculoproteins whose antigenic unit was 0.002 to 0.003 mgm. These figures, compared with 0.0002 mgm., which is the maximal protein content of one antigenic unit of *8* (in complement fixation), prove that its antigenic activity cannot be attributed to its contamination with proteins.

4. Antibody Production: Rabbits were examined for complement fixing antibodies with the five following tuberculosis antigens:

1. A crude alcoholic extract of tubercle bacilli.
2. Long and Seibert's tuberculin preparation KF_3, water-soluble and non-coagulable.

3. Two different protein fractions prepared by Dr. Johnson, nos. 304 and 502.

4. The antigen no. 8.

Only those rabbits were used whose serum did not show the slightest inhibition with any of the antigens.

In a series of previous experiments it had been ascertained that two intravenous injections of 0.5 mgm. (dry weight) of antigen *8* per kilo body weight would regularly produce strong complement-fixing antibodies. One-half milligram dry weight of *8* contains not more than 0.02 mgm. of protein. Five rabbits received 0.04 mgm. per kilo body weight

TABLE 3

RABBITS		ALCOHOLIC EXTRACT	502	304	KF 3	NO. 8: FULL DOSE	NO. 8: HALF DOSE	SERUM CONTROLS
	no.							
	59	−	−	++	−	−	−	−
Immunized with	60	−	−	+	−	−	−	−
304: 0.04 twice	62	−	−	−	−	−	−	−
	63	−	−	−	−	−	−	−
	74	−	−	−	−	−	−	−
	65	−	−	+	+	+	+	−
Immunized with	66	−	−	−	−	−	−	−
KF 3: 0.04 twice	67	−	−	−	++	−	−	−
	68	−	−	−	−	−	−	−
	69	−	−	−	−	−	−	−
	70	++	−	−	−	++++	++++	−
Immunized with	71	++++	−	++	+++	++++	++++	−
8: 0.5 twice	72	++++	−	+	+	++++	++++	−
	73	++++	−	−	−	++++	++++	−
	9	++++	−	−	+	++++	++++	−
Antigen control		−	−	−	−	−	−	−

of *304* intravenously twice, with an interval of 7 days, five received KF_3 in the same manner, and 5 received 0.5 mgm. dry weight of *8*. On the sixth day following the second immunization all 15 rabbits were bled and their sera tested again with the above-mentioned five antigens. Of each antigen one-half of the anticomplementary unit was used; *8* was also used in one-half of this dose. Table 3 shows the results.

Conclusions from Table 3: 1. Antigen *8* in the dose of 1 mgm. per kilo body weight regularly produces strong and specific complement-fixing antibodies in rabbits.

2. Two protein antigens have no appreciable antibody-producing effects on rabbits in doses which are equal to the double amount of protein which 1 mgm. of *8* may contain as contamination. In higher doses these proteins produce antibodies.

Again, it is hardly conceivable that the antigenic properties of *8* (in antibody production) could be attributed to its possible protein admixture.

In a second series of experiments the condition was made still more rigorous. Here it was assumed that all nitrogen of *8* is protein nitrogen. (This is certainly not the case.) Figuring that the average nitrogen-content of proteins is somewhere around 14 per cent, 1 cc. of *8* would contain approximately 0.68 mgm., and the amount of protein introduced by injecting 1 mgm. of *8* would be 0.068 mgm. Accordingly two rabbits were immunized with this amount of *304*, and two with the same amount of KF_3. They all failed to develop complement-fixing antibodies.

Antigen *8* is used at present as the antigen in our routine complement-fixation tests. In this character it seems to be about as good as the previously described alcoholic extracts.

5. Precipitation: Rabbits immunized with *8* develop readily precipitating antibodies, but not much attention has been given to this phase of the problem. Routine precipitation tests are being performed at the present time with the sera of our tuberculosis patients and with a number of nontuberculous patients. This part of the work will be reported after a sufficiently large number of sera has been examined to warrant a conclusion. It may only be mentioned that this is the first type of antigen with which an attempt at precipitation tests appeared not to be quite hopeless from the start.

6. Anaphylaxis: It was planned in this work to perform anaphylactic experiments, in order to exclude the possibility of protein contamination. It was found, however, that the anaphylactic reaction is by no means a delicate indicator for tuberculoproteins. In this respect there exists full agreement with previous workers (Baldwin (5), Krause (6), Friedberger and Mita (7)). The tuberculoproteins used in this work were apparently poorer anaphylactogens than the ones used by Krause. Krause found 1.6 mgm. of his extract-emulsion to be the minimal lethal dose; this amount would be represented in not less than 8 cc. of the antigen *8*, an amount which cannot be administered intravenously to a guinea pig without causing symptoms which would mask possible anaphylactic signs. As early as 1914 White (8) reported that he was not

able to elicit any anaphylactic reaction with alcohol-soluble substances of the tubercle bacillus. The opposite observations of Thiele and Embleton (9) on the alcohol-insoluble lipoids have never been repeated.

DISCUSSION

The preparation presented here is undoubtedly a true antigen, since upon injection into normal rabbits it readily produces antibodies with which it reacts in a specific way *in vitro*. That its antigenic action is not due to proteins is evidenced by the following observations:

First, the mode of its preparation is such as to make the presence of proteins highly improbable.

Second, the amount of protein that it may possibly contain, calculated on the basis of its nitrogen content, does not produce antibodies under identical conditions.

Third, its antigenic unit in complement fixation with human tuberculosis serum is smaller than that of any tuberculoprotein antigen reported in the literature or studied in my own work.

Fourth, the antibodies which it evokes are strictly specific and do not bind complement with tuberculoproteins.

Fifth, its antigenic potency increases with a decrease of its protein content.

It may, of course, be said that *8* may contain alcohol-soluble proteins which are not digested by trypsin, that they are present in minute traces, and that they are totally different from the tubercle-bacillus proteins which have been available in this work for comparative studies; and that exactly these proteins are endowed with all the antigenic properties described here. Nothing in this work excludes the possibility of such an objection, It is felt, however, that if such an objection be raised, the burden of proof rests on the objector.

As to the nature of the active principle nothing can be said but that it is apparently not a protein. It is obviously identical with the one in Petroff's alcoholic antigen, in Nègre and Boquet's *antigène méthylique*, and in Dienes and Schoenheit's specific alcohol-soluble substance. That alcohol-soluble substances of the tubercle bacillus may be antigenic has long been known (Citron and Klinkert, Kurt Meyer, Much, Dienes, *et al.*, etc.) Studies on the nature of their active principle have apparently not been done, with the exception of Petroff's (10) and Dienes and Schoenheit's (11). The latter have recently succeeded in splitting off from the purified alcohol-soluble antigen a substance which is highly

active *in vitro*, but inert *in vivo;* this substance is not a lipoid. Our present knowledge on the antigenic structure of the tubercle bacillus may be summarized as follows:

1. Proteins: They act as true antigens; all or some of them are endowed with tuberculin action; their importance in complement fixation with human tuberculosis serum appears to be far inferior to that of the alcohol-soluble substance. One can, however, produce artificial immune sera, with which they react up to high dilutions.

2. Alcohol-Soluble Substances: They are, as shown here, true antigens, very active *in vivo* and *in vitro*, but devoid of tuberculin action on tuberculous animals.

3. Carbohydrates (such as Zinsser and Mueller's (12) (13) (14) (15) (16) residue antigens, Laidlaw and Dudley's gum (17) and possibly Dienes and Schoenheit's nonlipoidal split-product): They are not true antigens, but haptens, since they do not produce antibodies in animals; they have no tuberculin action.

This brief review brings out the significant fact that there is a striking dissociation in the tubercle bacillus between the biologically and serologically active substances, as tested with natural tuberculosis serum, an observation which may greatly help to explain the relative failure of serological methods for the diagnosis and prognosis of tuberculosis.

From Zinsser's and his associates' work, it may be inferred that they believe that the residue antigen is the only serologically active group in the tubercle bacillus. Further studies will possibly show whether the *in vitro* active substance in the alcohol-soluble fraction is identical with the residue antigen or not. The fact that immune sera against tuberculoproteins do not react with the alcohol-soluble antigen, and that immune sera against the latter do not react with tuberculoproteins, seems to indicate at the present time that the tubercle bacillus contains more than one specific antigen.

SUMMARY

1. The alcohol-soluble, acetone and chloroform-insoluble substances of tubercle bacilli contain an active antigenic principle.

2. Evidence is presented that the antigenic action of these substances, whose chemistry is not known, is a nonprotein material.

I wish to acknowledge my thanks to Dr. William Charles White, Chairman of the Research Committee of the National Tuberculosis Association, through whose courtesy I obtained Dr. Johnson's and Dr. Long's bacillary fractions, and to Dr. T. B. Johnson and Dr. E. R. Long and Dr. F. Seibert for their kind permission to use their preparations in this work.

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THE ELIMINATION OF SPECIFIC SUBSTANCES OF THE TUBERCLE BACILLUS IN TUBERCULOUS ANIMALS[1]

J. FURTH

Recent studies indicate that immune animals acquire the power to fix antigen. This property of the immune organism, on the one hand, is obviously limited by the degree of immunity and, on the other hand, it can cause fixation only of a limited amount of toxic or other antigen. It is conceivable that in certain stages of diseases, such as tuberculosis, large amounts of the specific substances are eliminated.

Search for the soluble substances derived from tubercle bacilli was first attempted by Marmorek (1) by means of complement-fixation tests. Because of the interference of the urinary salts his method was abandoned.

Wildbolz (2) recommended the intracutaneous test with the urine of tuberculous individuals as a means of determining the activity of tuberculosis. The results obtained by this method have been contradictory. It was found that substances which produce skin reactions in tuberculous subjects are eliminated not only in tuberculosis but in many other diseases. There is little evidence to show that these substances are derived from tubercle bacilli.

The possibility of elimination of specific substances in tuberculous animals is intimately connected with the fate of the same substances when injected into normal or immune animals. Experiments in which the skin test has been used as a means of detecting the specific substances of tubercle bacilli will be discussed.

Franceschelli (3) injected normal rabbits and guinea pigs intravenously with tuberculin. He found that the tuberculin rapidly disappeared from the circulation and could be recovered from the urine.

Selter and Tancre (4) noted, two hours after injection of 0.5 to 1.5 cc. of tuberculin into normal guinea pigs, that more tuberculin entered the blood-stream and was eliminated than in tuberculous guinea pigs. On the other hand, two hours after injection the peritoneal cavity of tu-

[1] From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia.

berculous guinea pigs contained more tuberculin than the peritoneal cavity of normal guinea pigs.

Holst (5) injected 2 cc. of tuberculin into the peritoneal cavity of normal and tuberculous rabbits. He found that the disappearance of tuberculin was in all instances rapid and complete.

Similar experiments have been performed by Ornstein and Steinbach (6) and Dienes and Freund (7). Ornstein and Steinbach noted that tuberculin is eliminated more rapidly in tuberculous than in normal guinea pigs. Dienes and Freund, on the contrary, observed that large amounts of watery-extract were fixed at the site of inoculation although the animal died of tuberculin shock twelve hours after the injection.

Tuberculin, injected into the veins of tuberculous rabbits by Frisch and Silberstern (8), disappeared from the blood-stream more rapidly than that injected by Frisch and Klimersch (9) into the blood-stream of normal rabbits.

At the suggestion of Dr. Opie I have used the precipitation test as a means of detecting the specific precipitable substances of tubercle bacilli. Thus, several variable factors have been eliminated, and experiments on a larger scale were possible of performance with ease. Moreover, recent studies (11) (12) (13) indicate that substances probably polysaccharide in nature do not incite skin reactions in sensitive animals but can be identified by precipitation tests. Similar substances present in penumococci are known to be eliminated by the kidney in the course of pneumonia.

TECHNIQUE

Sera of rabbits, that were repeatedly injected with small does of living tubercle bacilli followed by large doses of dead tubercle bacilli, were used for the precipitation tests. Of the immune sera, 0.05 cc. gave a distinct turbidity with 0.0001–0.00005 cc. of tuberculin in 0.2 cc. physiological salt solution. Normal and tuberculous rabbits and guinea pigs were injected with a watery-extract of tubercle bacilli that was of approximately the same potency as tuberculin introduced into either the skin, peritoneal cavity or blood-stream. The blood and the urine of these animals were taken before the injection and at various intervals afterward. The urine was collected either by catheterization or from a metabolism cage. Before the tests, the urine was neutralized, heated to the boiling point and centrifugated until clear. By reason of this procedure no appreciable amount of the tuberculin present in the urine was removed from the urine. In the test for tuberculin 0.05 cc. of the immune serum was added to diminishing amounts of the fluid to be tested, brought to a volume of 0.2 cc. with physiological salt solution.

EXPERIMENTS ON RABBITS

The elimination of the injected precipitable substances of the tubercle bacilli was studied on 18 normal and 12 tuberculous rabbits. One series of rabbits, 4 tuberculous and 2 normal, was injected intravenously with

TABLE 1

Precipitation tests with the serum of rabbits injected with 1 cc. of water-extract of tubercle bacilli

	DILUTIONS OF THE SERUM											
	Normal rabbit						Tuberculous rabbit					
	1:1	1:3	1:10	1:30	1:100	1:300	1:1	1:3	1:10	1:30	1:100	1:300
Before injection	0	0	0	0			0	0	0	0		
10 minutes after injection	+	++	++	+	Tr.	0	+	++	++	+	Tr.	0
2 hours after injection	+	Tr.	Tr.	0			+	Tr.	Tr.	0		
7 hours after injection	0	0	0	0			0	0	0	0		
24 hours after injection	0	0	0	0			0	0	0	0		

Tr. = trace.

TABLE 2

Precipitation tests with the serum and the urine of a normal rabbit injected subcutanously with 2 cc. of Old Tuberculin in 10 cc. physiological salt solution

	DILUTIONS					
	Serum			Urine		
	1:1	1:2	1:4	1:1	1:2	1:4
Before injection	0	0	0	0	0	0
Serum 1 hour, urine 2 hours after injection	0	0	0	0	0	0
Serum 4 hours, urine 5 hours after injection	0	0	0	++	+	Tr.
Serum and urine, 10 hours after injection	0	0	0	++	+−++	Tr.−+
Serum and urine, 24 hours after injection	0	0	0	+	+	Tr.
Urine, 48 hours after injection	−	−	−	−	Tr.	−

Control test with old tuberculin: 1:100, ++; 1:200, ++; 1:500, ++; 1:1000, +; 1:2000, Tr.; 1:5000, Tr.; 1:10,000, negative.

Tr. = trace.

0.5 to 1.5 cc. of watery-extract in order to determine whether this antigen, like horse serum, persists in the circulation of the normal animal but disappears from the circulation of the immune animal (Opie (10)). We found that the injected precipitable substances of bacilli disappeared rapidly from the circulation of both normal and tuberculous rabbits. Table 1 illustrates this observation.

Another series of rabbits (3 normal and 1 tuberculous) was injected subcutaneously with 0.5 to 2 cc. of Old Tuberculin. No tuberculin was found in the serum of these animals when tested at varying intervals following the injection, but it could be recovered from the urine of the animals (table 2).

The most probable explanation of the foregoing observations is that the elimination of the injected specific precipitable substance goes hand in hand with resorption, so that in the blood-stream it never reaches a concentration strong enough to be detectable by the method used in this study.

We believe, in agreement with Franceschelli (3), that the rapid elimination of tuberculin is sufficient to explain its inability to form antibodies.

In the case of the above tests the objection may be raised that, even in well-immunized animals, the amount of antigen injected has been too large to be fixed. The advisability of injecting as small amounts of tuberculin as possible is obvious. Unfortunately, after the injection of less than 0.1 cc. of tuberculin it cannot be identified in the urine with certainty by the method used in these tests.

Seven normal and 7 tuberculous rabbits, in groups of two, consisting of one normal and one tuberculous animal, were injected with 0.1 to 0.5 cc. of tuberculin subcutaneously. Slightly delayed and diminished elimination was found three times in the tuberculous and four times in the normal animal. This result can be explained by individual variations and technical errors.

Another objection might be that rabbits are rather unfavorable subjects for the demonstration of the fixation of tuberculin, inasmuch as they do not produce antibodies against tuberculin in detectable amounts, and that, furthermore, they frequently do not exhibit a specific inflammatory reaction when injected with tuberculin. On account of this second objection we continued our studies with guinea pigs.

EXPERIMENTS ON GUINEA PIGS

Experiments similar to those described above were carried out on guinea pigs. After the injection of less than 0.1 cc. of tuberculin the urine of the animals gave uncertain results when tested for tuberculin with strong precipitating immune serum. Therefore, in subsequent studies 0.1 to 0.2 cc. of tuberculin was injected. Eight normal and 6 tuberculous guinea pigs were injected with 0.1 to 0.2 cc. of tuberculin

intracutaneously or intraperitoneally. The urine, eliminated during the first 24 hours following the injection, was collected, except in a few instances in which specimens were examined after 6, 24 and 48 hours. The 6- and 24-hour specimens contained only traces of the precipitable substances of tubercle bacilli, and the bulk of this substance was found in the urine collected between 6 and 24 hours after injection. When the quantity of this substance present in the urine is estimated on the basis of the precipitation tests and when the amount of urine eliminated is also considered, there is no marked difference between normal and tuberculous animals.

One series of guinea pigs in groups of two (one normal and one tuberculous) received from 0.5 to 1 cc. of tuberculin in the peritoneal cavity. The serum of these animals was taken by means of cardiac punctures made at varying intervals following the injection. The appearance and disappearance of the precipitable substance present in the tuberculin was then determined. In three tests the sera of the tuberculous guinea pigs gave slightly weaker reactions, while in one instance there was no noticeable difference.

DISCUSSION

Evidence presented by Opie (10) shows that skin sensitiveness to proteins is due to an antibody which localizes the antigen at the site of introduction. Antigen in limited amount is fixed in immune animals, but its elimination might occur if an excess is administered. Since little is known concerning antigen and antibody in relation to the tuberculin reaction, their relation to the auto-urine reaction, discussed by Wildbolz, is uncertain, and elimination of tuberculin by tuberculous individuals need not be regarded as paradoxical.

The rapid elimination of the precipitable substance of the injected tuberculin explains perhaps its inability to produce antibodies (Franceschelli).

Judging from analogous conditions it is probable that certain specific substances of tubercle bacilli are eliminated during certain stages of tuberculosis. While the substances which produce the specific skin reactions are, to a certain extent, fixed in animals which react to them, the specific precipitable substances are in no appreciable amounts localized when introduced into the body of tuberculous animals. The detection of specific precipitable substances in the urine of tuberculous animals is dependent upon the sensitiveness of the method used. The smallest

amount of tuberculin detectable by means of precipitin has been 0.00005 cc. Tests with the urine of a small number of tuberculous animals gave, as might be expected, negative results.

Improvements in the technique of precipitation tests for antigens present in the urine may prove to be of practical value in detecting the activity of tuberculous processes.

Chemical differences between the precipitable substances of tubercle bacilli and those producing skin hypersensitiveness have been recently described by Laidlaw and Dudley (11), Mueller (12) and Long and Seibert (13). According to these investigations there is a gum-like substance in the tubercle bacillus which is precipitable but gives no skin reaction, and another substance, probably a protein or protein derivative, which gives the skin reaction.

CONCLUSIONS

1. The precipitin reaction may be used to study the elimination of specific substances of the tubercle bacillus from the animal body.

2. The smallest amount of tuberculin, which, when injected into normal or tuberculous guinea pigs, can be detected as precipitable substance in the urine of the animal, is 0.1 cc.

3. The precipitable substance present in tuberculin, when injected into the vein of normal or of tuberculous rabbits, rapidly disappears from the circulation and can be recovered from the urine of the animal.

4. When tuberculin is injected into the subcutaneous tissue of normal or tuberculous rabbits the precipitable substance is not present in the blood-stream in detectable amounts, but it can be recovered from the urine of the animals.

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